DELAWARE HOSPITAL ISSUE

DELAWARE STATE MEDICAL JOURNAL

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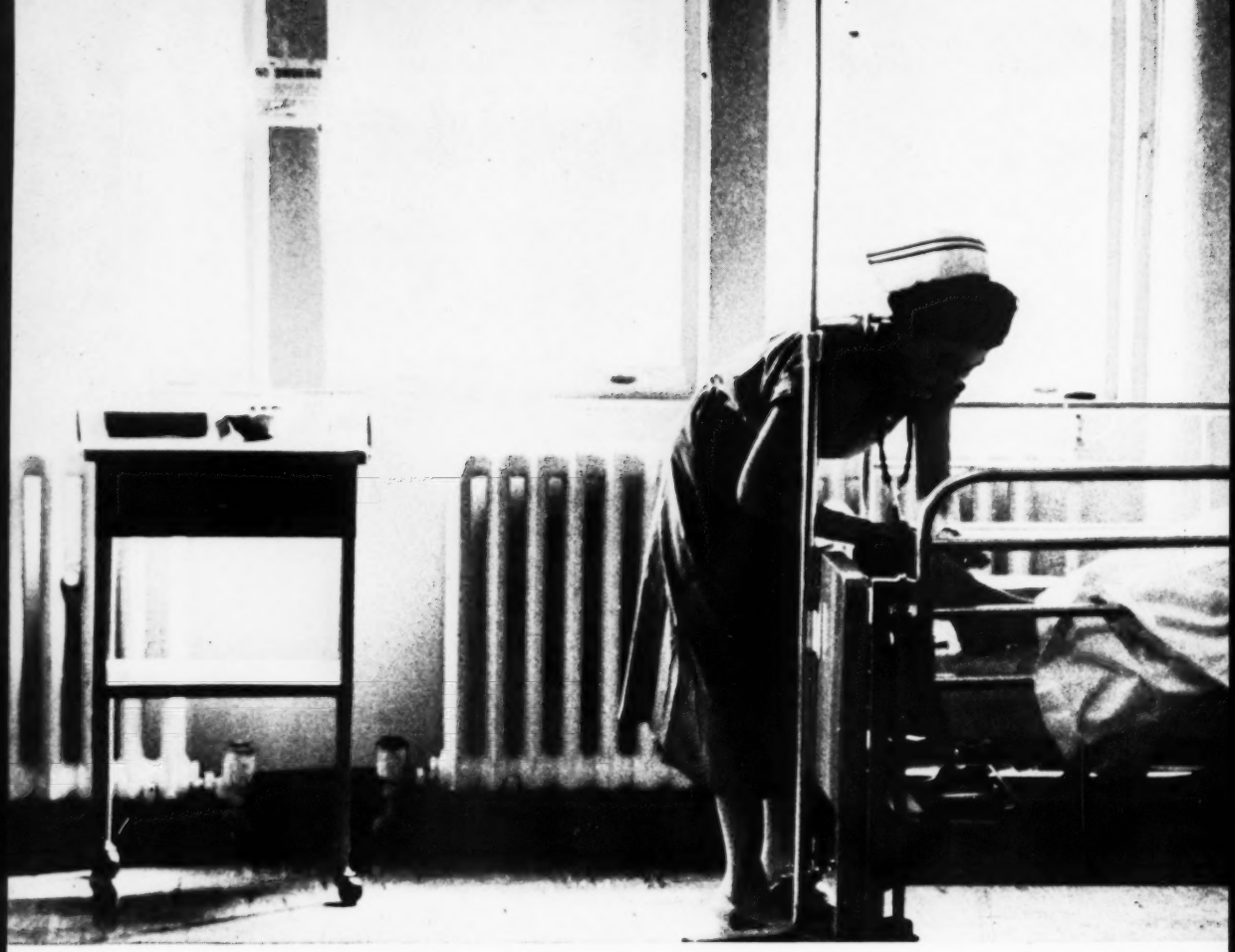
VOLUME 31 JULY, 1959 NUMBER 7

CUSHING'S SYNDROME

SECONDARY TO FOCAL ADRENAL CORTICAL HYPERPLASIA

ANNUAL MEETING OCT. 15
WILMINGTON, DELAWARE



wherever STAPHYLOCOCCI PRESENT A PROBLEM

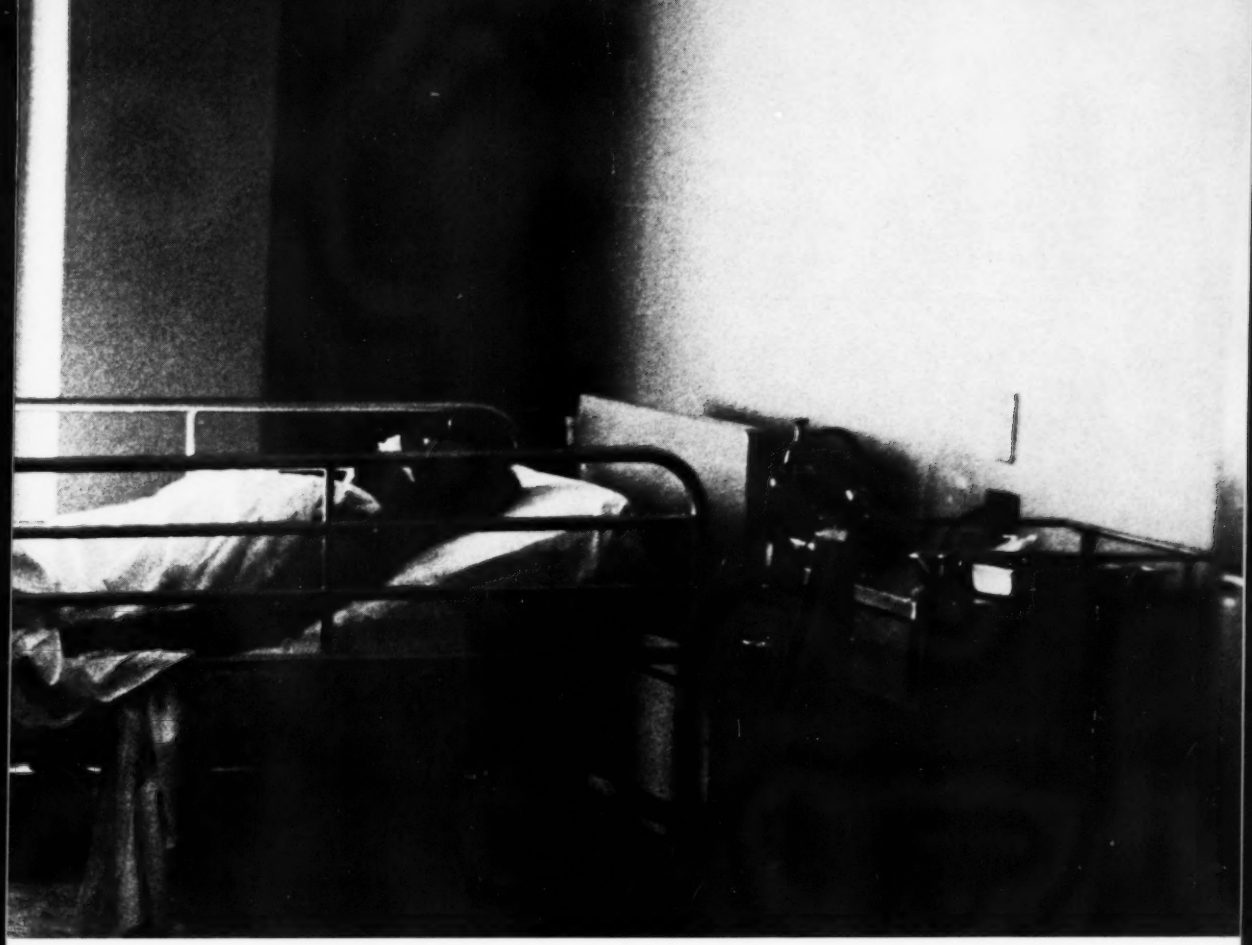
CHLOROMYCETIN

Increased incidence of staphylococcal infections has been reported for Europe, Britain, Australia, New Zealand, and the Americas.[1-5] World-wide reports indicate that many strains responsible for these infections are resistant to commonly used antibiotics.[1-3,5-14] However, this ubiquitous pathogen, according to studies from Germany,[8] Canada,[9] Uganda,[10] New Zealand,[11] England,[12] and the United States,[13,14] remains sensitive to CHLOROMYCETIN.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

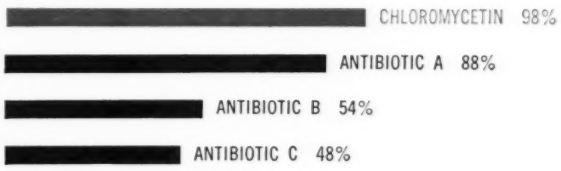
CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Smith, I. M.: Staphylococcal Infections, Chicago, Year Book Publishers, Inc., 1958, p. 21. (2) Pryles, C. V.: *Pediatrics* **21**:609, 1958. (3) Monro, J. A., & Markham, N. P.: *Lancet* **2**:186, 1958. (4) Purser, B. N.: *M. J. Australia* **2**:441, 1958. (5) Williams, R. E. O., in National Conference on Hospital-Acquired Staphylococcal Disease, Sept. 15-17, 1958, Atlanta, Georgia, U.S. Dept. Health, Education, and Welfare, Communicable Disease Center, 1958, p. 11. (6) Rountree, P. M., & Beard, M. A.: *M. J. Australia* **2**:789, 1958. (7) Mudd, S.: *J.A.M.A.* **166**:1177, 1958. (8) Fischer, H. G.: *Deutsche med. Wchnschr.* **84**:257, 1959. (9) Royer, A., in Welch, H. & Marti-Ibañez, E.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 783. (10) Hennessey, R. S. E. & Miles, R. A.: *Brit. M. J.* **2**:893, 1958. (11) Markham, N. P., & Shott, H. C. W.: *New Zealand M. J.* **57**:55, 1958. (12) Oswald, N. C.; Shooter, R. A., & Curwen, M. P.: *Brit. M. J.* **2**:1305, 1958. (13) Suter, L. S., & Ulrich, E. W.: *Antibiotics & Chemother.* **9**:38, 1959. (14) Borchardt, K. A.: *Antibiotics & Chemother.* **8**:564, 1958.

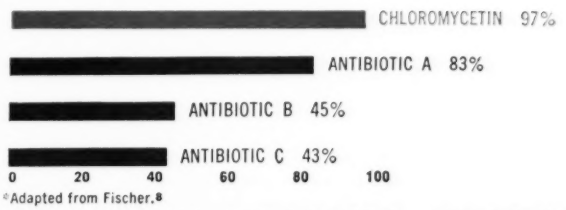


IN VITRO SENSITIVITY OF STAPHYLOCOCCI, FROM TWO SOURCES, TO CHLOROMYCETIN AND TO THREE OTHER ANTIBIOTICS*

HOSPITAL PATIENTS (201 strains)



UNIVERSITY CLINIC PATIENTS (209 strains)



*Adapted from Fischer.[8]

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MEDICAMENTA VERA

DELAWARE STATE MEDICAL JOURNAL

Owned and published by the Medical Society of Delaware, a scientific non-profit corporation. Issue the fifteenth of each month under the supervision of the Committee on Publication:

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CONTENTS

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Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, Published by the American Medical Association, Chicago.

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(tablets and drops)

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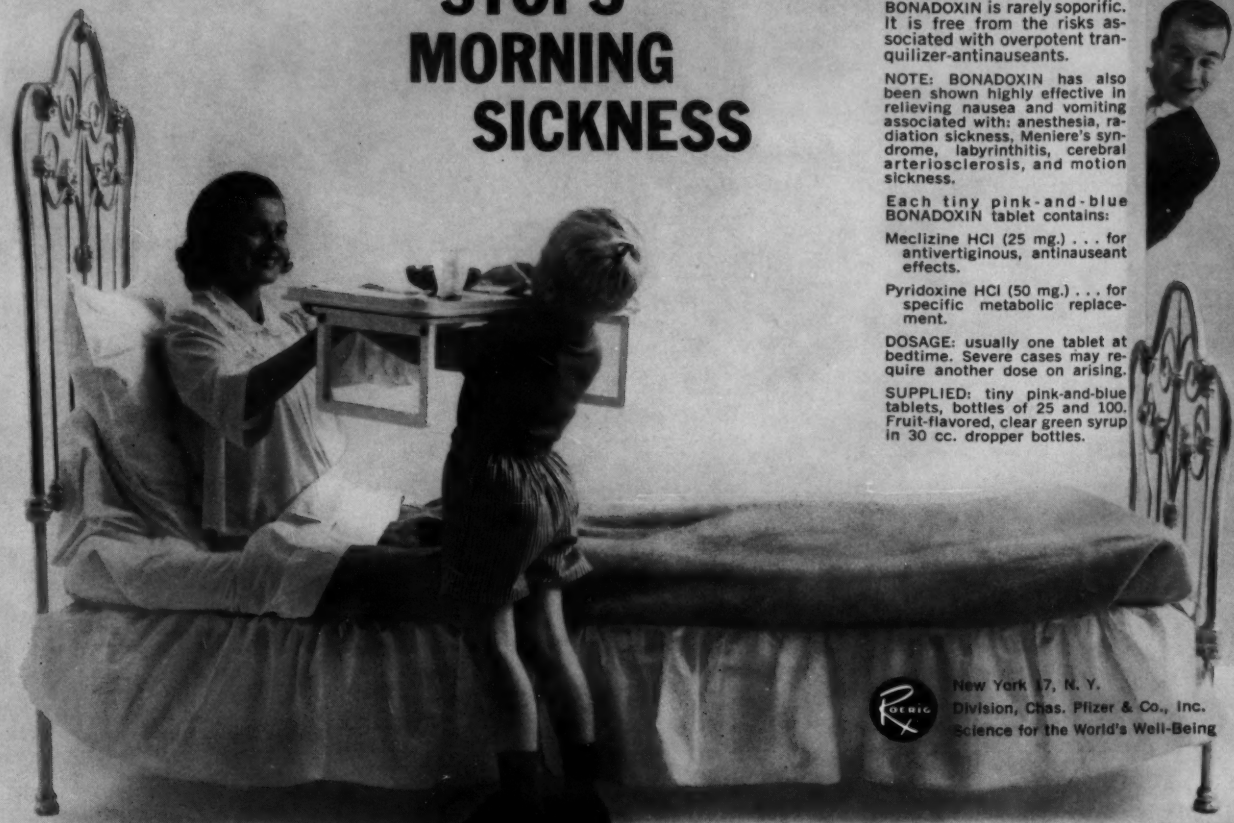

BONADOXIN Tablets relieve nausea and vomiting of pregnancy in 9 out of 10,[1-7] often within a few hours.

Moreover, a controlled study of 620 cases reported that with BONADOXIN "toxicity and intolerance [are] zero."[1] BONADOXIN is rarely soporific. It is free from the risks associated with overpotent tranquilizer-antinauseants.

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Each cc. contains:
Meclizine dihydrochloride . . 8.33 mg.
Pyridoxine hydrochloride . . . 16.67 mg.

Dosage:

under 6 months	0.5 cc.	2 or 3 times daily, on the tongue, in fruit juice or water
6 months to 2 years	1.5 to 2 cc.	
2 to 6 years . .	3 cc.	
adults and children over 6	1 tsp. (5 cc.)	

References: 1. Goldsmith, J. W.: Minnesota Med. 40:99 (Feb.) 1957. 2. Groskloss, H. H., et al.: Clin. Med. 2:885 (Sept.) 1955. 3. Weinberg, A., and Werner, W. E. F.: Am. Pract. & Digest Treat. 6:580 (April) 1955. 4. Crawley, C. R.: West. J. Surg. 8:463 (Aug.) 1956. 5. Tartikoff, G.: Clin. Med. 3:223 (March) 1955. 6. Dunn, R. D., and Fox, L. P.: Clinical exhibit. 7. Codling, J. W., and Lowden, R. J.: Northwest Med. 57:331 (March) 1958. 8. Dougan, H. T.: Personal communication. 9. Leonard, C. L.: Personal communication. 10. Steinberg, C. L.: Personal communication.

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The pain went away fast—in just 15 minutes—and I was back on the job the next morning! But not one 9B customer came in the whole day!

Percodan®-Demi & Percodan® *Tablets*

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ACTS FASTER — usually within 5-15 minutes. **LASTS LONGER** — usually 6 hours or more. **MORE THOROUGH RELIEF** — permits uninterrupted sleep through the night. **RARELY CONSTIPATES** — excellent for chronic or bedridden patients. **VERSATILE** — new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

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AND THE PAIN WENT AWAY FAST

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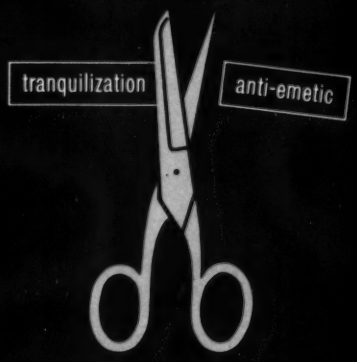
now potent tranquilizer therapy is safer than ever



Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action – divorced from such "diffuse" effects as anti-emetic action.

MELLARIL is virtually free of such toxic effects as

- jaundice
- Parkinsonism
- blood dyscrasia

"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

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specific, effective tranquilizer • safer at all dosage levels

remarkable lack of side effects

In more than 3,000 carefully-followed patients, Mellaril has been almost completely free of such major side effects as jaundice, extrapyramidal symptoms, Parkinsonism, blood dyscrasia, dermatitis– **even when given in quantities far in excess of the usual dosage.**

"POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."[2]

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."[3]

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."[4]

ABSENCE OF SIGNIFICANT SIDE EFFECTS

"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."[1]

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."[5]

NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."[6]

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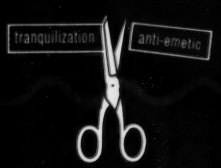
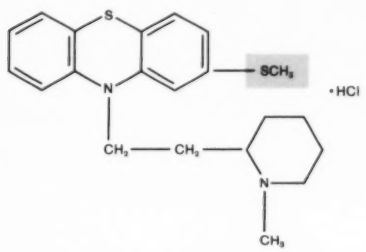
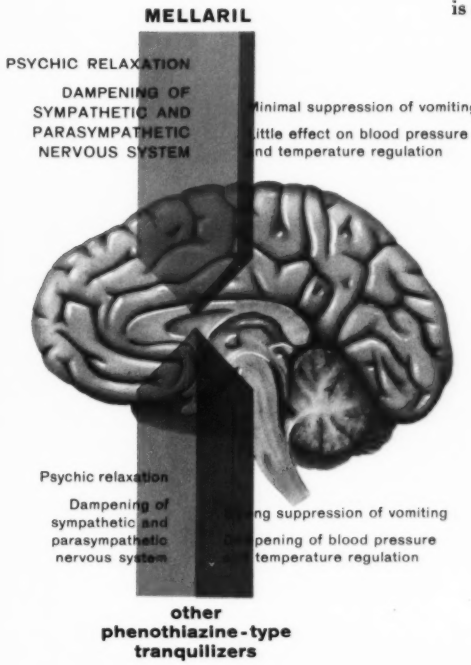


a new advance in tranquilization:
greater specificity of tranquilizing action plus fewer side effects



Of 109 phenothiazines synthesized by Sandoz, Mellaril was selected as the most promising on the basis of extensive evaluation. The presence of a thiomethyl radical ($S\text{-}CH_3$) in the position conventionally occupied by a halogen in other phenothiazines is unique and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.



2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.

3 A notable absence of extrapyramidal stimulation.

4 Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.

5 Virtual freedom from toxic effects — jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

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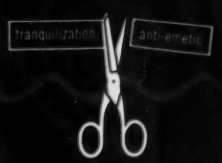

excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY "... produced extremely satisfactory results in the broad therapeutic range represented in this series."[3]

POTENT AGENT "... appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent. . . . It is effective in a variety of psychiatric disorders, including schizophrenic reactions. . . . The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."[6]

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."[7]

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life . . . were treated with Mellaril at the dosage level of 10 mg. three times daily. In 94 such patients, 83 obtained an excellent therapeutic response."[8]

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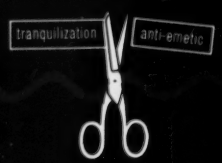

"... extremely satisfactory results..."
in a clinical spectrum ranging from
minor nervous disorders to
severe psychotic disturbances[3]

RESULTS WITH MELLARIL IN 194 PATIENTS[3]

ACUTE PSYCHOTICS	CHRONIC PSYCHOTICS	NEUROTICS
83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

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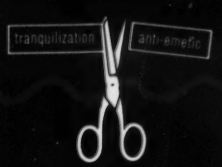

a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS		
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN		
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. *115*:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. *88*:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

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Of course, women like "Premarin"®

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs nursing—"Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

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- permits **greater latitude** in adjusting dosage to minimum level needed for maintenance, because ARISTOCORT and chlorpheniramine are supplied in the **lowest dose tablets available** for each component alone
- supplies **ascorbic acid** for increased demand in stress conditions

Indications: *Generalized pruritus of allergic origin; hay fever, allergic rhinitis, perennial asthma, seasonal and perennial rhinitis, vasomotor rhinitis; drug reactions and other allergic conditions.*

Dosage: *One to eight capsules a day in divided doses. Dosages should be established on the basis of individual therapeutic response.*

Precautions: *Drowsiness may occur, and is usually due to the antihistamine effect. Occasionally this may also cause vertigo, pruritus and urticaria. Because of the low dosage, side effects with* ARISTOMIN *have been relatively infrequent and minor in nature. However, since* ARISTOCORT *Triamcinolone is a highly potent glucocorticoid with profound metabolic effect, all precautions and contraindications traditional to corticosteroid therapy should be observed. Discontinuance of therapy must not be sudden after patients have been on steroids for prolonged periods. It must be carried out gradually over a period of as much as several weeks.*

Further information available on request.

Supply: *Each* ARISTOMIN *Capsule contains:*

ARISTOCORT® *Triamcinolone*	*1 mg.*
Chlorpheniramine Maleate	*2 mg.*
Ascorbic Acid	*75 mg.*

Bottles of 30 and 100

References: *1. Maurer, M. L.: Clinical Report, cited with permission. 2. Levin, L.: Clinical Report, cited with permission. 3. Gaillard, G. E.: Clinical Report, cited with permission.*

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(lung x 65, injected with carbon-gelatin)

comments by clinical investigators:

"I would conclude that ARISTOMIN *is truly a worthwhile aid in treating allergic problems."*[1]

"The results have been uniformly good. The patients have stated that their symptoms were very much relieved. I have not encountered any side reactions except from one patient, who complained of some drowsiness, which I attribute to the antihistamine."[2]

"In general . . . it [ARISTOMIN] *is an excellent product. Over-all, it appears to be more effective than any simple antihistamine we have used. Despite the fact that we employed it in the treatment of a variety of nonselected individuals and problems, we had excellent and good results in 25 of the 39 patients."*[3]

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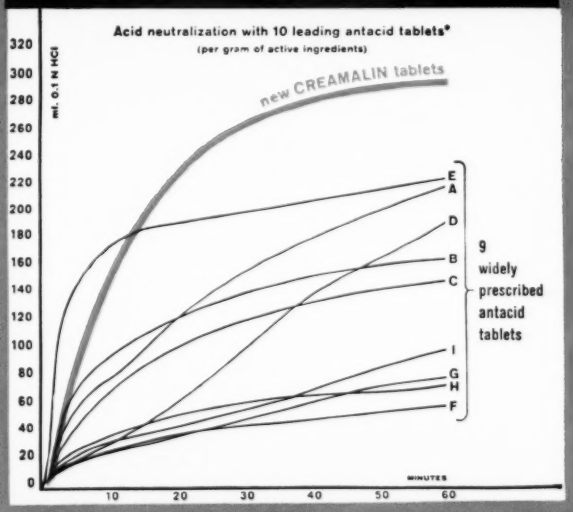

Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

CREAMALIN NEUTRALIZES *MORE* ACID *LONGER*

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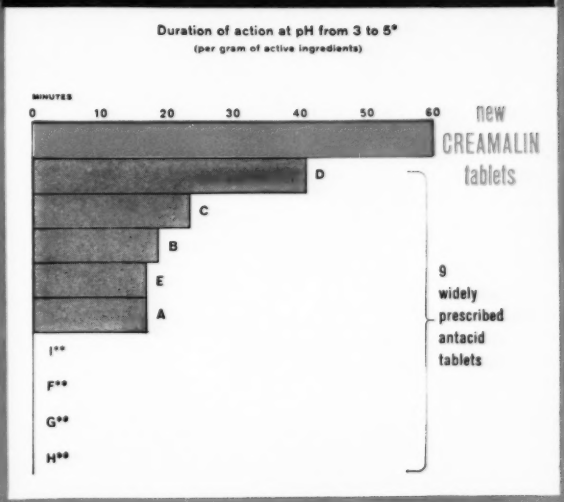

*Hinkel, E. T., Jr., Fisher, and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
**pH stayed below 3.

Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydroxide.

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3. *Neutralizes acid longer (more lasting relief)*
4. *No constipation • No acid rebound*
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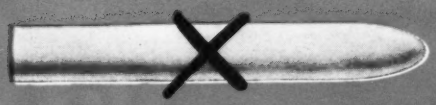

No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

Adult Dosage: Gastric hyperacidity—2 to 4 tablets as necessary. Peptic ulcer or gastritis—2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

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SPRAINS

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FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

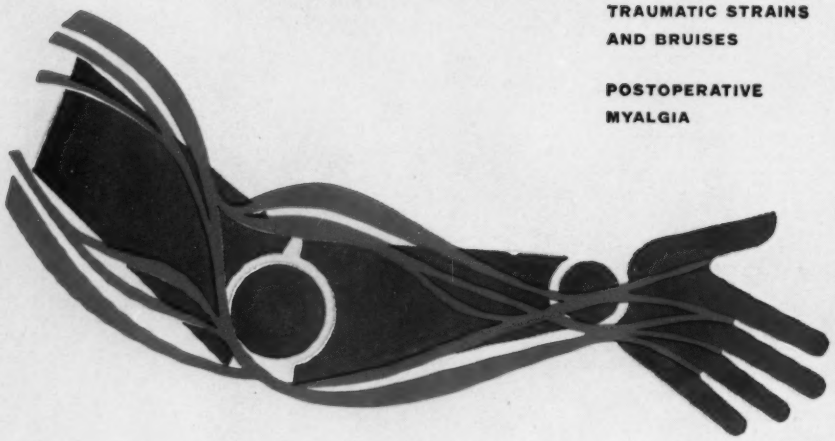
DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS AND BRUISES

POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

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when pollen allergens attack the nose...

Triaminic provides more effective therapy in respiratory allergies because it combines two antihistamines[1,2] with a decongestant.

These antihistamines block the effect of histamine on the nasal and paranasal capillaries, preventing dilation and exudation.[3] *This is not enough;* by the time the physician is called on to provide relief, histamine damage is usually present and should be counteracted.

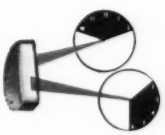
The decongestive action of orally active phenylpropanolamine helps contract the engorged capillaries, reducing congestion and bringing prompt relief from nasal stuffiness, rhinorrhea, sneezing and sinusitis.[4,5]

TRIAMINIC is orally administered, systemically distributed and reaches *all* respiratory membranes, avoiding nose drop addiction and rebound congestion.[6,7] TRIAMINIC can be prescribed for prompt relief in summer allergies, including hay fever.

References: 1. Sheldon, J. M.: Postgrad. Med. **14**:465 (Dec.) 1953. 2. Hubbard, T. F. and Berger, A. J.: Annals Allergy p. 350 (May-June) 1950. 3. Kline, B. S.: J. Allergy **19**:19 (Jan.) 1948. 4. Goodman, L. S. and Gilman, A.: Pharmacol. Basis Ther., Macmillan, New York, 1956, p. 532. 5. Fabricant, N. D.: E.E.N.T. Monthly **37**:460 (July) 1958. 6. Lhotka, F. M.: Illinois M.J. **112**:259 (Dec.) 1957. 7. Farmer, D. F.: Clin. Med. **5**:1183 (Sept.) 1958.

Triaminic®

TRIAMINIC provides around-the-clock freedom from hay fever and other allergic respiratory symptoms with just one tablet q. 6-8 h. because of the special timed-release design.



Each TRIAMINIC timed-release tablet provides:
Phenylpropanolamine HCl.....50 mg.
Pheniramine maleate.....25 mg.
Pyrilamine maleate.....25 mg.

Also available: TRIAMINIC SYRUP for those patients of all ages who prefer a liquid medication. Each 5 ml. teaspoonful is equivalent to ¼ Triaminic Tablet or ½ Triaminic Juvelet. TRIAMINIC JUVELETS provide half the dosage of the Triaminic Tablet with the same timed-release action for prompt and prolonged relief.

STOP *running noses* *and open stuffed noses orally*

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capsules—14 VITAMINS AND 11 MINERALS

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Remarkable relief from

LOW BACK PAIN

and

DYSMENORRHEA

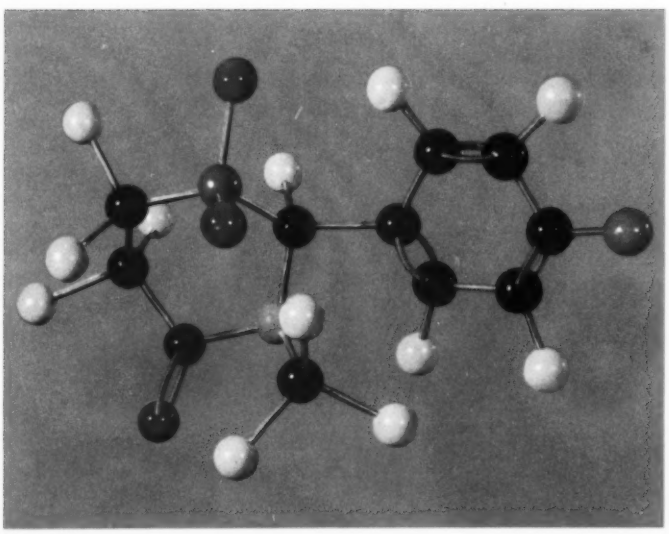
Trancopal®

*the first true tranquilaxant**

***Potent* MUSCLE RELAXANT**

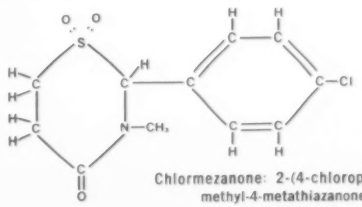
***...Equally effective as a* TRANQUILIZER**

***tran-qui-lax-ant** (tran'kwi-lak'sant) [< L. tranquillus, quiet; L. laxare, to loosen, as the muscles]



Trancopal, a major development of Winthrop research, is a new, orally administered non-hypnotic central relaxant and tranquilizer. It relieves muscle spasm in a variety of musculoskeletal and neurologic conditions and also exerts a marked tranquilizing effect in anxiety and tension states.

Unrelated chemically to any other drug in current use, Trancopal offers a completely new major chemical contribution to therapeutics.



Chlormezanone: 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1-dioxide

Clinical studies of over 4400 patients by 105 physicians[1] proved Trancopal remarkably effective in musculoskeletal conditions, anxiety and tension states.

MUSCULOSKELETAL DISORDERS

effective in

93%

of 1570 documented cases of

LOW BACK PAIN

(LUMBAGO, SACROILIAC DISORDERS)

By relieving muscle spasm and pain, Trancopal permits early and active exercise and physical therapy to accomplish maximal benefits for rapid recovery.

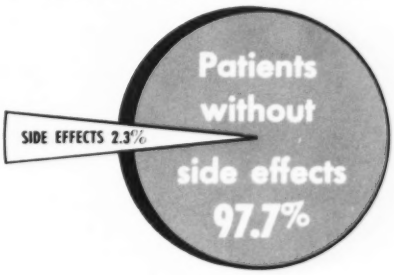
Trancopal

the first true tranquilaxant

BETTER TOLERATED AND SAFER THAN OLDER DRUGS[1]

With Trancopal there is no clouding of consciousness, no euphoria or depression. Even in high dosage, there is no perceptible soporific effect. Because it does not irritate gastric mucosa, it can be taken without regard to mealtimes. Administration does not hamper work—or play. Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. Toxicity is extremely low. And Trancopal has a lower incidence of side effects than has zoxazolamine, methocarbamol or meprobamate.

INCIDENCE OF SIDE EFFECTS WITH TRANCOPAL IN 4483 PATIENTS



ANXIETY AND TENSION STATES

effective in 88% of 443 documented cases of DYSMENORRHEA

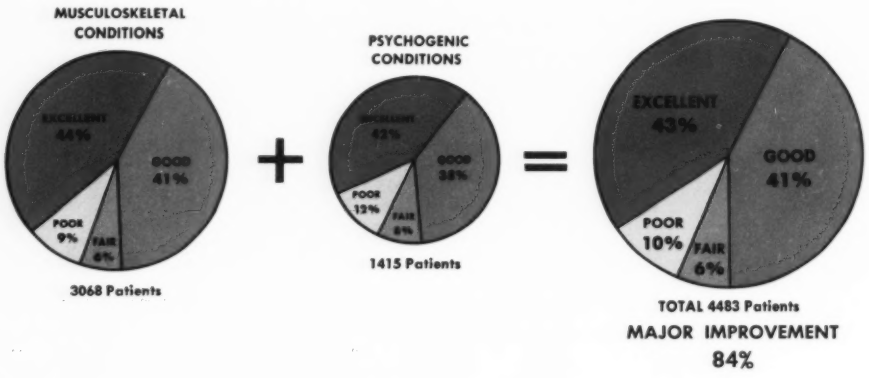
AND PREMENSTRUAL TENSION

Because of its exceptional calmative property, Trancopal "... allows the patient to use his energies in a more productive manner in overcoming his basic problems."[2]

Dosage: 100 to 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Thoroughly evaluated clinically...

Clinical studies of 4483 patients by 105 physicians[1] have demonstrated that Trancopal often is effective when other drugs have failed. From these studies it is evident that Trancopal can provide more help for a greater number of tense, spastic, and/or emotionally upset patients than can any other chemotherapeutic agent in current use.



INDICATIONS

Musculoskeletal

- Low back pain (lumbago)
- Neck pain (torticollis, etc.)
- Bursitis
- Rheumatoid arthritis
- Osteoarthritis
- Disk syndrome
- Fibrositis
- Ankle sprain, tennis elbow, etc.
- Myositis
- Postoperative muscle spasm

Psychogenic

- Anxiety and tension states
- Dysmenorrhea
- Premenstrual tension
- Asthma
- Angina pectoris
- Alcoholism

Supplied: Trancopal Caplets® (scored) 100 mg., bottles of 100.

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MUSCLE RELAXANT
...Equally effective as a
TRANQUILIZER

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What's Your Corticosteroid Score?

		True	False
1	Corticosteroids relieve rheumatic pain by raising the pain threshold.	☐	☐
2	Corticosterone is the only corticosteroid identified in adrenal venous blood.	☐	☐
3	Approximately 10 mg. of urinary 17-ketosteroids are excreted daily during normal adrenocortical function.	☐	☐
4	The pioneer experiments on the effects of adrenalectomy were performed by Addison.	☐	☐

For answers to quiz, see opposite page.

corticosteroid quiz

scores highest in clinically important tests

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prednisone

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answers: 1. False—by altering tissue reaction. 2. False—only hydrocortisone has been so identified. 3. True. 4. False—performed by Brown-Sequard.

DELAWARE STATE MEDICAL JOURNAL

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CUSHING'S SYNDROME SECONDARY TO FOCAL ADRENAL CORTICAL HYPERPLASIA

Case Report of Successful Surgical Treatment by Bilateral Total Adrenalectomy

GERHARD HARTENAUER, M.D.*

CLARENCE E. GRAYBEAL, M.D.**

The purpose of this paper is to record our experience in diagnosis and treatment of a patient with Cushing's syndrome, to discuss the interesting aspects of his pre- and post-operative management, and to describe and document the patient's response to therapy.

PRESENTATION OF CASE

This was the first admission to the Delaware Hospital of an 18 year old factory worker who had been referred because of high blood pressue, unexplained pains in both legs and suspicion of some endocrinological disorder.

Approximately five to six years prior to this admission there was a gradual onset of fullness and redness of the face and increasing obesity of the trunk. During the last two years multiple purple cutaneous striae were discovered around the shoulders, lower abdomen, flanks and buttocks. Besides the change in his physical status, there were emotional and mental disturbances in that he became lethargic, bashful and inactive. There was lack of interest in the usual activities of his age group. Libido was strictly denied.

Physical examination revealed a short boy 61½ inches in height weighing 187 pounds. The pulse was 130 and regular. The respiratory rate was 24, the temperature 99°F, and the blood pressure 220/160. The patient had the typical moon-face with plethoric cheeks. The neck was short and had the characteristic cervico-dorsal buffalo hump. The trunk indicated marked centripetal obesity, while the extremities retained their normal configuration. Dark purplish striae were seen around both shoulders, lower abdomen, flanks and buttocks. Acne vulgaris lesions were present over the anterior chest wall. The breasts had a typical female form and consistency. The penis was of almost normal size, but buried in a big fat pad, while the testicles were rather small. The heart was slightly enlarged to the left. The lungs were normal to percussion and auscultation. No abdominal masses could be palpated. Fundoscopic exami-

*Chief Resident in Medicine, Delaware Hospital
**Chief Resident in Surgery, Delaware Hospital

nation indicated grade 2 focal and generalized narrowing of the arteries of scattered flame-shaped hemorrhages and exudates. The remainder of the physical examination was within normal limits.

The clinical diagnosis was substantiated by the following studies:

1. SPECIAL INVESTIGATIONS

A. Urinary hormone assay studies for 17-ketosteroids and 17-hydroxycorticoids, ACTH test included.

Two 24 hour urine specimens were collected in order to determine the base-line urinary excretion of the 17-ketosteroids and 17-hydroxycorticoids. During the following two days 25 units of ACTH were given intravenously over a period of 8 hours, and the same hormone levels were determined in two 24 hour urine specimens. The hormone assay studies were completed by a final investigation on the day following the ACTH test. The circulating eosinophile count was studied simultaneously.

Urinary Hormone Assay Studies

	17-Ketosteroid	17-Hydroxycorticoids	Circulating Eosinophile Count
Baseline	30.2 mg/24 hrs.	16.0 mg/24 hrs.	37
Baseline	18.0 mg/24 hrs.	12.0 mg/24 hrs.	6
ACTH Test	43.0 mg/24 hrs.	56.0 mg/24 hrs.	0
ACTH Test	68.0 mg/24 hrs.	72.0 mg/24 hrs.	0
Post-ACTH Test	48.0 mg/24 hrs.	32.0 mg/24 hrs.	19

Normal levels for 17 ketosteroids range between 9 and 22 mg. per 24 hours and for 17 hydroxycorticoids between 2 and 9 mg/24 hrs.

B. Blood plasma steroid studies for 17 hydroxycorticoids
Only Baseline Studies:
1. 40 Gamma per 100 cc. of Plasma
2. 27 Gamma per 100 cc. of Plasma
Normal level: 6-15 Gamma

C. Urinary hormone assay studies for estrogens and pituitary gonadotrophin.
Pituitary Gonadotrophin (FSH, LH)
8 - 24 Mouse Units/24 hours
Normal level: 4 - 35 Mouse Units/24 hours
Estrogens
67 - 133 Mouse Units/24 hours
Normal level: 13-27 Mouse Units/24 hours

This is not a diabetic type glucose tolerance curve, demonstrating that the carbohydrate metabolism was not yet affected by the disease process.

2. ORAL GLUCOSE TOLERANCE TEST

	Fasting	30 min.	1 hour	2 hours	3 hours	4 hours
Blood	77 mg.%	171 mg.%	186 mg.%	116 mg.%	90 mg.%	49 mg.%
Urine	Neg.	Neg.	1 plus	Neg.	1 plus	Neg.

3. OTHER LABORATORY STUDIES

BLOOD

RBC 5,700,000 per cmm.
HGB 16.5 gm., 105%
HCT 55%

Reticulocyte Count 1.4% of total RBC

WBC 10,300 per cmm.
74% polys, 21% lymphs, 5% mono.

Circulating Eosinophile Count 37

Platelets 289,000

Total Blood Volume 4485 cc. or 57 cc/kg.
Total Plasma Volume 2437 cc. or 31 cc/kg.
Red Cell Mass 2048 cc. or 26 cc/kg.
Body Hematocrit 45.6%

URINALYSIS

Sp. Gr. 1.010
Trace of albumin
Acid reaction
RBC 1-3
WBC 4-8

CHEMISTRY

BUN 12 mg. per 100 cc.
CO_2 25 mEq. per liter
Chloride 99 mEq. per liter
Sodium 139.5 mEq. per liter
Potassium 4.1 mEq. per liter
Calcium 11 mg. per 100 cc.
Phosphorus 2.9 mg. per 100 cc.
Cholesterol 322 mg. per 100 cc.
Total Serum Protein 6.5 gm. per 100 cc.
Serum Albumin 3.5 gm. per 100 cc.
Serum Globulin 3.0 gm. per 100 cc.

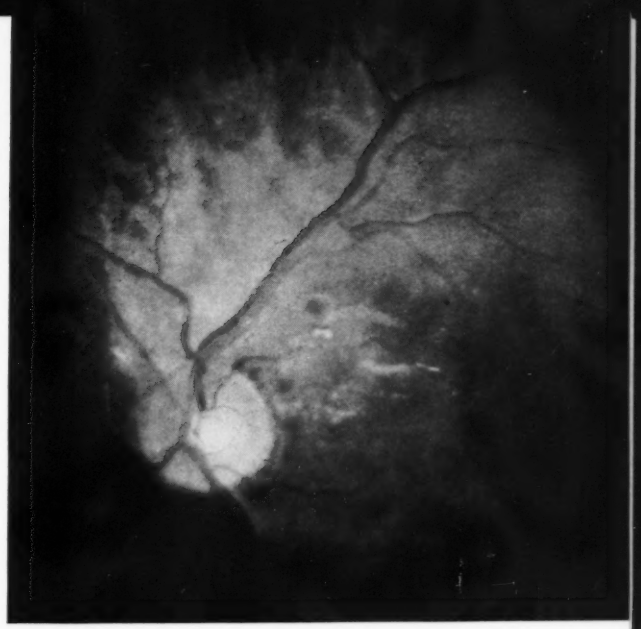
The above figures demonstrate that there was no evidence of hypokalemic alkolosis, hypernatremia, polycythemia, or lymphopenia. The eosinopenia is of paramount importance for the diagnosis. The urine was acid at every examination.

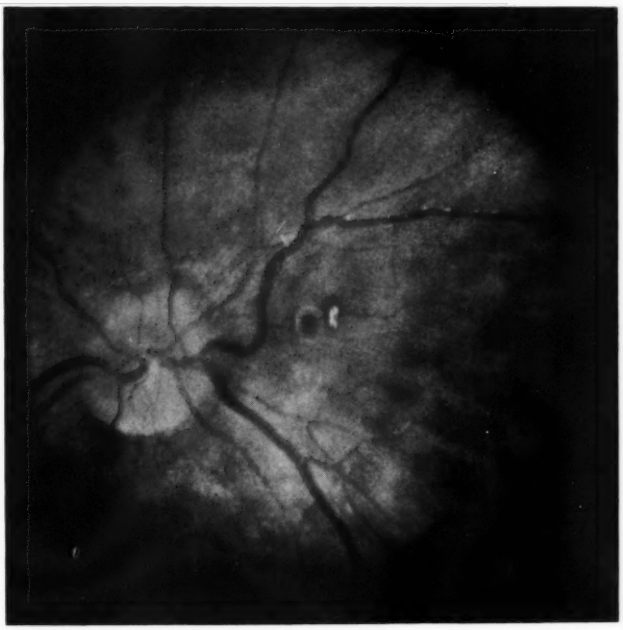
4. Evaluation of the Cardiovascular System

An electrocardiogram indicated left ventricular hypertrophy and sinus tachycardia of 130. Preoperatively, the blood pressure fluctuated between 160 and 220 systolic, and between 130 and 160 diastolic. A ballistocardiogram was consistent with a grade II abnormality.

5. Radiographic Investigations

Roentgenological examinations of the cervical, dorsal and lumbar spine, wrist, knees and ankle indicated mild to moderate generalized osteoporosis but no pathological fractures. A presacral air





EYE GROUNDS

ON ADMISSION

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study with oxygen visualized only the right adrenal gland which appeared to be normal in size and configuration.

A chest x-ray demonstrated normal diaphragm, heart, mediastinum and lung fields. An intravenous pyelogram was essentially normal.

PREOPERATIVE MANAGEMENT

After the clinical diagnosis of Cushing's syndrome, secondary either to bilateral idiopathic adrenocortical hyperplasia or to simple hyperfunction of a normal adrenal gland, had been supported by the above described special investigations, it was decided to perform a bilateral total adrenalectomy. Preoperatively, the patient was carefully reevaluated by determining hemoglobin, hematocrit, BUN, sodium, potassium, chloride, CO_2 calcium and phosphorus. The day prior to surgery the patient received 300 mg. of cortisone at 10 a.m. and 100 mg. of cortisone at 9 p.m. intramuscularly. On the next day, shortly before the patient was taken to the operating room, another intramuscular injection of 100 mg. of cortisone was given. A gastric tube was passed and connected to a suction apparatus. For preoperative sedation, 75 mg. of Demerol and 0.04 mg. of scopolamine were administered. A cutdown was performed as a precautionary measure.

OPERATIVE REPORT

The anesthesia was induced with sodium pentathol and after intubation the anesthetic consisted of cyclopropane and ether which was given by endotracheal tube. The patient was then turned on his right side and a hypobaric nupercaine spinal anesthesia was performed to alleviate any undue sympathetic response when manipulating the adrenal gland. At the onset of the operation the blood pressure was 190/130 but fell to 150/100 after the induction of anesthesia. The spinal anesthesia caused a fall of the blood pressure to 90/60, and neosynephrine was given intravenously in order to stablize the blood pressure level. The left adrenal was approached first through a lumbar kidney incision. Gerota's fascia was entered and the adrenal gland located without difficulty, as the kidney was dissected downward through a thick layer of perirenal fat. The gland itself appeared of normal size and no adenomata were palpable. After ligation of the gland's blood supply, it was totally removed without difficulty. The operative site was drained, several through and through #30 stainless steel wire retention sutures were placed and the wound finally closed with interrupted chromic catgut sutures on the muscle and fascial layers.

The blood pressure, which had remained steady at about 150/120, fell to 100/70 after the left adrenal gland had been totally removed. 100 mg. of Solu-cortef was administered and the blood pressure rose to 140/90. The patient was then turned and the right adrenal was approached through an incision similar to that of the opposite side. The moment the right adrenal artery was ligated, the blood pressure fell to 60/30, but it quickly recovered after neosynephrine support and remained at about 100/60. The excision of the right adrenal gland offered no more difficulty than the left one. It also appeared normal in size and no adenomata were palpable. No accessory adrenal tissue was visualized. The closure was similar to that of the opposite side.

The patient was kept in the recovery room for 50 minutes at which time his blood pressure was 140/104, the pulse was 100 and regular, the respiratory rate was 24, and the temperature was 101.6°.

PATHOLOGY FINDINGS

The left adrenal weighed 9 grams and measured 7.5 x 3 x 1.5 cm. The cortex appeared yellowish with orange mottlings and measured 3 mm. in thickness.

The right adrenal weighed 7 grams. It measured 5 x 5 x 2.5 x 1 cm. The cut sections showed a yellow-orange cortex which was 2 to 3 mm. in thickness. Together the glands weighed 16 grams.

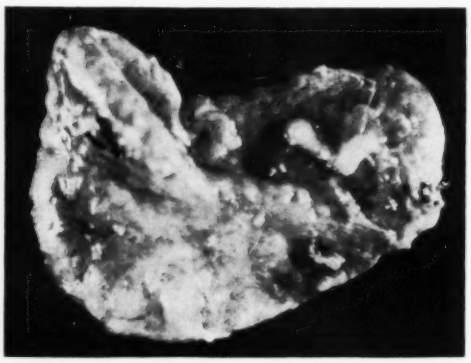


Figure 1: Right Adrenal

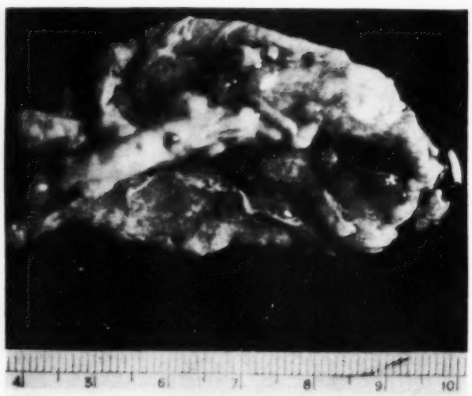


Figure 2: Left Adrenal

There was no configuration to suggest adenomatous hyperplasia in their gross description. (Fig. 1 and Fig. 2).

Microscopically there appeared to be minimal cortical thickening, with the zona fasciculata being mainly involved. With hematoxylin and eosin stain, the outer portion of the zona fasciculata appeared as a rather irregularly edged area of clear cells which were pale staining. A deeper inner zone of more granular appearing cells was noted which stained deeper with hematoxylin and eosin, and cell cords were somewhat thickened.

Both zones varied considerably in thickness within the same gland, and the junction point between the clear cells and the more granular cells in the cortex was rather indefinite. In some foci an apparent abrupt demarcation could be seen. Most of the substance of the cortex was composed of the darker granular cell layer.

The zona glomerulosa was difficult to visualize, being extremely narrow in most sections, and completely missing or compressed in others. Where the zona glomerulosa was missing, the outer clear cells of the zona fasciculata appeared to extend all the way to the capsule. The zona reticularis was not altered in these glands.

Although adenomata were not observed grossly, there were a few circumscribed collections of cells in the zona fasciculata. These were arranged in a micronodular pattern when viewed under the microscope. They measured only a few millimeters in diameter, showed no encapsulation and occasionally contained mixtures of large granular as well as clear cells. An interesting finding was prominent infiltration of the deeper portions of the zona fasciculata and zona reticularis by groups of fat cells. Focal collections of lymphocytes and plasma cells were found in the interstitial spaces of the cortex and may have been related to recent surgery.

HISTOLOGICAL DIAGNOSIS

In summary, microscopic findings were consistent with multiple foca of adrenal cortical hyperplasia with focal fat infiltration and chronic adrenalitis. (Fig. 3, Fig. 4, Fig. 5, Fig. 6)

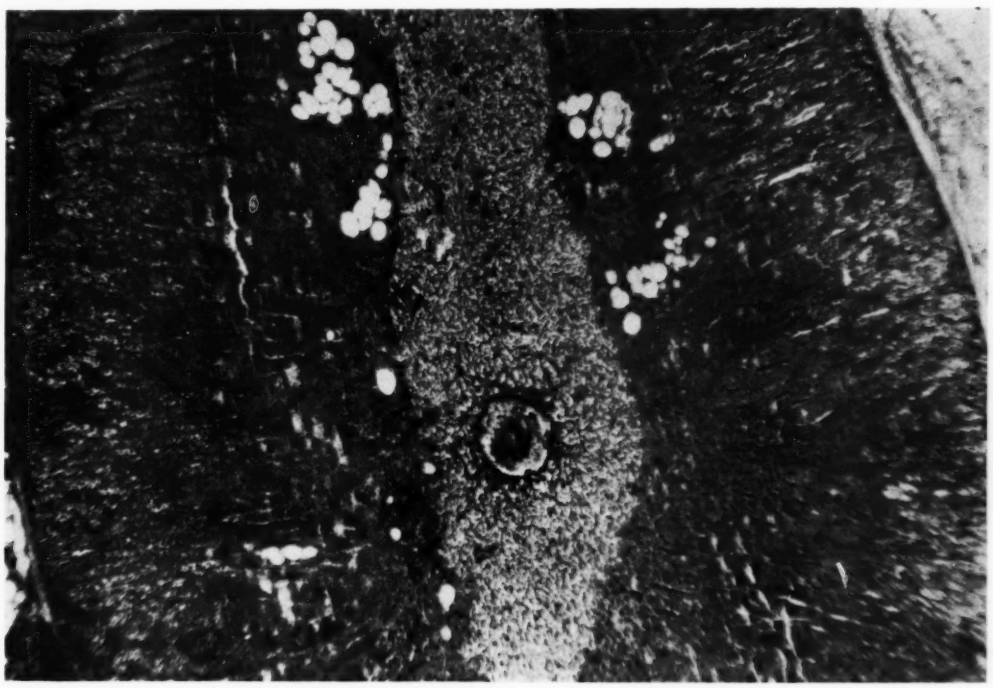


Figure 3 (X 25): Narrow to absent zona glomerulosa. Increased thickness and breadth zona fasciculata. Fat infiltration of zona reticularis and deep portion zona fasciculata.

Figure 4 (X 75):

Markedly narrowed, focally absent zona glomerulosa. Increased depth and width of cords of cells in zona fasciculata with increased granularity deeper portion.

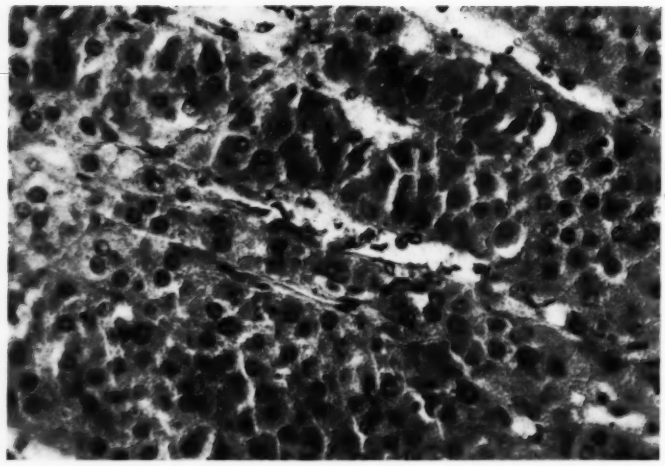


Figure 5 (X 320):

Medial portion zona fasciculata showing slight hypertrophy of cell cords and marked granularity of cytoplasm.

Figure 6 (X 75):

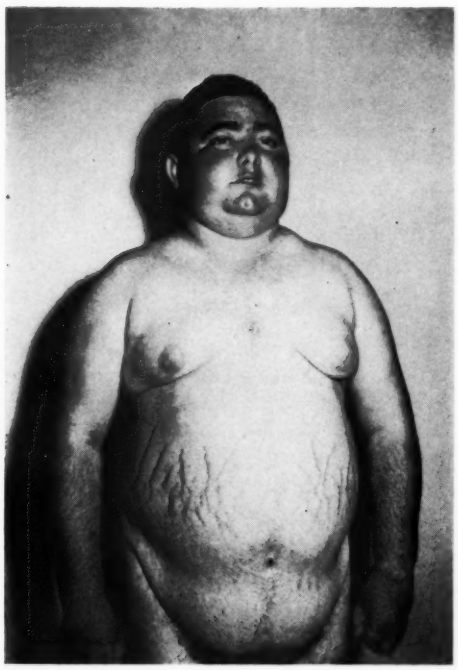
Non-encapsulated cortical nodule composed of mixture of vacuolated and granular cells.

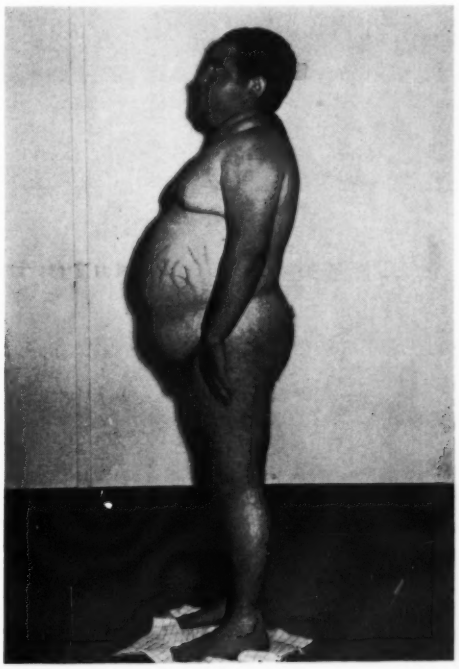
POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Several days postoperatively, a subcutaneous infection of the posterior portion of the left wound became evident. This condition was treated by removing several skin sutures to allow more adequate drainage. A penicillin resistant, hemolytic Staphylococcus aureus was cultured from the wound. Irrigation with neomycin solution was carried out and kanamycin, 250 mg. was administered every six hours for seven days. With the above mentioned treatment, the infection subsided gradually, the wound granulated and healed within two and one-half weeks. The right wound remained free from infection, but the skin reflected delayed wound healing by taking twice as long to heal as the skin of a normal individual.

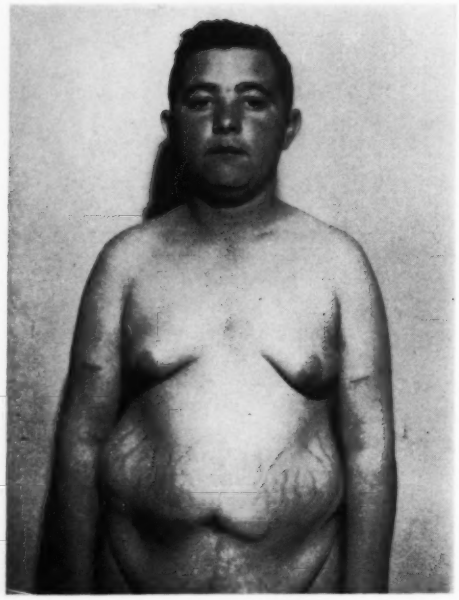
The postoperative management of the patient's electrolyte status by substitutional steroid therapy wih cortisone and desoxycorticosterone (DOCA) and by sodium chloride administration was completely dependent on the sodium, chloride, potassium and CO_2 determinations and on early signs and symptoms of adrenal insufficiency. The patient was discharged five weeks after the bilateral adrenalectomy and his substitutional steroid therapy consisted at that time of 25 mg. of cortisone twice daily and 5 mg. of DOCA sublingually every other day.

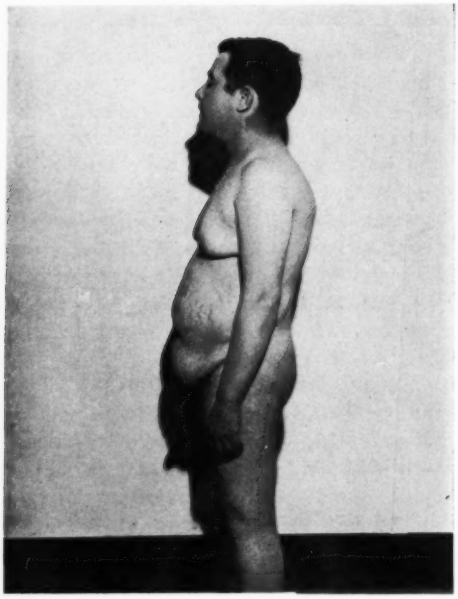
Postoperatively, the skin of the face became dry, erythematous and itchy. Superficial layers were shed in the form of fine dry scales. This skin condition lasted for about three weeks. Brown pigmentation of the operative scars or other portions of the body described by many authors was not seen. The well-described "cortisone withdrawal syndrome" was apparent in our case. The symptoms of this syndrome consisted of anorexia and vomiting early in the morning, abdominal discomfort, low-grade





ON ADMISSION: Note the round face, short neck, buffalo hump, multiple striae, acne vulgaris lesions over the anterior chest, centripetal obesity sparing the limbs increased growth on limbs and buttocks. Figures 7 and 8.





FIVE MONTHS AFTER SURGERY: Note the weight loss of 46 pounds and marked diminution of the above described signs. Figures 9 and 10.

fever, tachycardia, weakness and restlessness. The mental state changed quite frequently during these episodes from one of excellent cooperation to that of reluctance and resentful ill-humor.

LONG TERM MANAGEMENT

The initial dosages of cortisone and DOCA were gradually decreased over many weeks, even temporarily to levels considered too low for substitutional therapy.

The replacement therapy currently consists of 12.5 mg. of cortisone twice daily and 0.1 mg. of fluorocortisone (Florinef) every other day orally. Electrolytes are checked periodically and have been stable now for several months.

PRESENT STATUS

The tremendous improvement in this patient's condition can be documented by the striking change in the physical findings, by the reversal of a hypertensive blood pressure level of 260/160 to a normotensive level of 128/82, by the weight loss of 46 pounds, by the remarkable improvement of the hypertensive eye ground changes, by the striking disappearance of all mental abnormalities, and by the return of the ECG to normal. The striae have faded but are still visible. Prognostically, there is good reason to assume that this patient will continue to improve.

SUMMARY

An 18 year old boy is presented who exhibits a typical history and the characteristic physical findings of Cushing's syndrome. The diagnosis is substantiated by urine and plasma-hormone assay studies and other laboratory procedures. Most important aspects of the preoperative management, surgical procedure, and postoperative care are discussed. The approach to the maintenance level of steroid replacement therapy is described.

Finally, the patient's present status is summarized as a documentation of the successful therapy for Cushing's syndrome by bilateral total adrenalectomy.

PRACTICAL ASPECTS OF BLOOD GROUPING IN PATERNITY SUITS

● **A brief review of genetics will aid in examining blood group determinations and their application in paternity suits.**

With the blood group systems known today, approximately 100,000 different blood types can be identified although only a few of these systems are of use medico-legally.

The day will come when an individual's blood group will be as distinctive as his fingerprints.

MARVIN SHUSTER, M.D.*

Fifteen states† have enacted laws accepting blood grouping as evidence in disputed paternity suits. The infallibility of blood grouping is becoming more generally recognized. Since Landsteiner's identification of the A and B blood factors, much progress has been made with the discovery of many more blood group systems and numerous statistical studies establishing their inheritance patterns. These blood group systems include the following: ABO, MNSs, Rh, Kell, Duffy, Kidd, Pp, Lutheran, Lewis and Levay. At present only a few of these blood group systems are of use medico-legally. Eventually, sufficient blood groups may be recognized that an individual's blood will be as distinctive as his fingerprints. With the blood group systems known today, approximately 100,000 different blood types can be identified[1].

Unlike many physical traits, blood groups cannot be altered. The antigens, determined serologically, are present at birth on and in the red blood cells. These facts are obviously important medico-legally. In addition to disputed paternity proceedings, blood grouping tests are also of value in cases of derivative citizenship[2], "exchanged"

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baby cases, personal identification and examination of blood stains.

Serologic determination of blood groups depends on antigen-antibody interaction. Antigens (blood factors) are present on the red blood cell. Potent and specific antibodies (in antisera) must be available for identification of the corresponding antigens. This may be done by direct interaction or indirectly as in the Coomb's test. The technical procedures involved are beyond the scope of this paper.

To understand the practical use of blood grouping tests in such cases as disputed paternity suits, one must have good comprehension of the genetic processes involved. Genetics is the science of heredity and hereditary transmission of various body traits or properties. The individual receives factors from his parents. Each human cell, except the germ cell, contains 46 chromosome—23 pair. One chromosome of each pair is derived from the mother and the matching chromosome from the father. Mature sperm and ova have 24 chromosomes and during fertilization, the combining of sperm and ovum gives the full chromosomal complement to the new individual.

Chromosomes are composed of complex yet specifically arranged proteins in chain-like arrangement. Genes may be considered as unique arrays of amino acids and other organic compounds situated at specific loci on the chromosome. This can be visualized as a string of beads. The genes are responsible for the various properties as hair color, body habitus, iris color and many others including, of course, the blood types. Genes occurring at the same locus on matching chromosomes are called alleles when they are determinants of different qualities of a given trait. Thus the genes determining blue or brown irides are alleles. A dominant gene is one which finds outward expression or can be easily determined. Recessive genes may or may not be expressed in a visible or easily determined trait or property. A dominant gene with its matching recessive gene will often give rise to the outward appearance of the characteristic determined by the dominant gene. Although this is true of such things as hair color and iris pigmentation, it does not entirely hold true in blood grouping. This will be discussed later.

The outward expression of gene make-up is called the phenotype. Genotype is more specific and indicates the exact gene composition of an individual for given properties. Where the genotype consists of two identical genes, it is called homozygous. Homozygosity, therefore, can occur with two dominant or two recessive genes. If dominant and recessive genes are present at the same locus of matching chromosomes, the individual is heterozygous.

The ovum and sperm each carry only one of each chromosomal pair. A heterozygous individual has, potentially, two different types of germ cells he (or she) can produce. This can be illustrated using the ABO blood group system as an example. Both A and B genes are dominant and O gene is recessive. These genes transmit the corresponding named antigen (agglutinogen) found on the red blood cells. A person designated as A blood type may be either homozygous or heterozygous. That is, he may have two A genes or an A and an O gene. This is also true of B blood type. A person with O blood type is of necessity homozygous. Type AB individuals are heterozygous and have both an A and a B gene.

This brief review of genetics will aid in examining blood group determinations and their application in paternity suits.

ABO System

The same basic rules of inheritance obtain when using this blood group system.

1. A and B genes are dominant.
2. O gene is recessive.
3. An individual with O type of blood cannot be a parent of an AB type child.
4. An AB type person cannot be a parent of a child with O type blood.
5. A or B genes can be present in the child only if present in one of the parents.

From these thoroughly accepted rules, a chart may be constructed with all possible ABO group matings to determine possible ABO types of children, or conversely, given blood type of mother and child, we can exclude certain blood types in a man designated as the father.

Several alleles of A type are known and these give rise to subgroups of A known as A_2, A_3, A_4, A_5 and A_0. Tests for the subgroups of A are not sufficiently reliable for medical-legal work. Their use would increase the number of exclusions of paternity by only 1%. In a wrongly accused male, the ABO system can be expected to prove non-paternity in 18% of cases, according to Wiener[4].

MNSs System

The MN system is genetically simple. More recently two allelic genes called S and s were found to be closely associated with genes M and N. However, because of scarcity of potent and reliable S and s antisera, testing for these antigens is best deleted in the seroliogic workup of disputed paternity cases. In contrast to other gene pairs, both M and N are dominant. Three serologic types are recognized: M, N and MN. These phenotypes are also expressions of the genotype. The basic rules of inheritance in this system are:

1. Each parent contributes only one gene, either M or N.
2. An M parent cannot have a child of Type N.
3. An N parent cannot have a type M child.

When testing erythrocytes for these antigens, it is important to include suitable known control cells of types M, N and MN. Use of two or more different antisera also is recommended. A chart similar to the ones made for the ABO system can also be constructed for the MN system. Using this system alone, wrongly accused individuals may be excluded in 18% of such cases.

RH System

In the Rh system of blood groups, the alleles are designated by English serologists and many American workers as Cc, Dd, Ee. This nomenclature is easier to work with than the more cumbersome terminology of Wiener in which Rh and hr are followed by various subscripts and superscripts. The question of nomenclature is still unsettled and the reader is referred to the report of the latest American Medical Association's Committee on Medico-legal Problems[5] for more information on this matter. Antisera are currently available for all antigens except that designated d. For that reason we cannot give exact genotypes for bloods that are phenotype D. Tables are available[6] indicating probable genotypes of these individuals. There is perhaps a 10% error in using these tables.

General rules to be applied to the Rh blood group system are:

1. C can appear in a child only if present in one of the parents.
2. Antigen c can appear in a child only if present in a parent.
3. D is present in a child only if one or both parents have D type.
4. E can be present in a child only if parent or parents have E type.
5. Antigen e, similarly, must be present in one or both parents to be found in the child.

The above rules are an oversimplification of the inheritance of the Rh blood group factors. Gene deletions have been known to occur as have variants of C antigen. Wiener estimates that use of Rh blood system alone will result in exclusion of 25% of unjustly accused men.

Other Blood Group Systems

Numerous other blood group systems are known and their inheritance patterns have been fully established. Their inclusion in blood grouping workups in medico-legal situations is not recommended. Reasons against their use is, (1), poor supply of potent antisera, (2), weakly antigenic factors producing equivocal results and, in many systems, statistically few cases where

any benefit would be derived. These blood group systems include Kell-Cellano, Lutheran, Duffy, Kidd, Lewis, Levay, Pp and some other obscure ones.

Adjuvant Determinations

Individuals are divided into secretors and non-secretors of A, B and H substance[8]. It is known that A and B substance are widely distributed in the body cells and secretions. Secretors of A blood type secrete A substance in their saliva and those of B blood type secret B substance in their saliva. Individuals of O blood type secrete H substance. Both A and B blood type individuals who are secretors also secrete H substance. Anti-H serum is available and can be used to determine whether a person is or is not a secretor. Known secretor and non-secretor salivas should be run simultaneously. Allelic genes S and s (*not* related to the MN system) are said to control this trait. Capability to secrete is considered dominant. Approximately 80% of all individuals are secretors. This can be helpful in paternity suits since a secretor child of a non-secretor mother cannot have a non-secretor father. This determination is not recommended for medico-legal use at present.

Precautions in Medico-legal Applications of Blood Grouping

All parties concerned in the disputed paternity case, mother, child and accused man, must be definitely identified before serological determinations are carried. This can be done through fingerprints, photographs and signatures, but the best method is mutual identification of the individuals Competent laboratories must be employed. The AMA Committee on Medico-legal Problems have set forth the criteria of an expert in blood grouping[9]. It is better to have two independent laboratories perform the blood grouping determinations. Technically, proper control cells must be used along with the red cells of the parties concerned. More than one serum should be used in testing for each antigen. All medico-legally accepted blood groups must be tested for.

DISCUSSION

There are two types of exclusion of paternity. One is the "failure to inherit" in which a child does not have a factor that is present in the putative father. In this case, we must know the man's genotype relative to any given blood group. A simple example of this type of exclusion is a child of type O and mother of type O where the putative father is type AB. Where this man the father, the child must be either type A or B.

The other type of exclusion is the "appearance of a strange factor" not present in either mother or accused man. Thus a child group A and mother group O cannot have a father of group O.

It is obvious that only results indicating exclusion of paternity are of medico-legal importance. Reports of the serological laboratory are best recorded in chart form giving name of individual tested, date, examiner and positive or negative designation under each of the factors tested. Interpretation should read only "exclusion of paternity" or "non-exclusion of paternity." Results showing non-exclusion of paternity should not be presented in court since this might serve to prejudice a jury.

Overall, using only ABO, MN and Rh blood grouping systems, a wrongly designated man will be excluded in over 50% of cases. Exclusions are not the sum of exclusions in each blood group since simultaneous exclusions may occur in more than one. Exclusion on the basis of more than one blood group factor is no more meaningful than exclusion by a single blood factor.

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ACUTE MYOCARDIAL INFARCTION MASKED BY BOTH LEFT BUNDLE BRANCH BLOCK AND DELIRIUM TREMENS*

● **The electrocardiogram is the time-honored method in the diagnosis of myocardial infarction. Recently, SGO-T determinations have been used in confirmation. In the interesting case reported here, the accuracy of both of these tests has been impaired by other factors and the diagnosis was made largely on clinical grounds.**

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GERALD A. BEATTY, M.D.‡
J. RICHARD DURHAM, M.D.‡

In 1954, La Due, Wroblewski and Karmen[1] were the first to establish the value of the serum transaminase (SGOT) level as a diagnostic measure for acute myocardial infarction. The result of their research on this subject stimulated others to begin probing deeper into the value of the serum transaminase test as an index of liver cell injury[2]. Numerous other conditions were shown by Lieberman, et al[3] to be associated with normal values of SGOT unless acute damage to cardiac, hepatic or striated muscle tissue was involved.

Since SGOT is present in all human sera and in various tissues, particularly heart muscle, liver, skeletal muscle and kidney, sufficient necrosis of any of the above may cause a rise in serum SGOT levels. Shields and Shannon[4] reviewed 29 patients having one or more SGOT levels greater than 400 units. There were eight cases of primary liver disease with a transaminase range between 490 and 2150 units, the average being 1027 units.

The remaining 21 cases were divided into three groups: (1) in the first group were three cases which exhibited acute congestive hepatomegaly without clinical or electrocardiographic evidence of myocardial infarction. The SGOT levels in these patients ranged from 700 to 3000 units, with an average of 1510. (2) in the second group were nine cases exhibiting definite clinical and electrocardiographic evidence of acute myocardial infarction and passive conges-

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tion of the liver. The peak SGOT levels in this group ranged from 430 to 2050 with an average of 886. (3) In the third group were nine cases showing definite clinical and electrocardiographic evidence of acute myocardial infarction without clinical evidence of enlarged or tender liver. In this group the peak SGOT levels ranged from 400 to 675 with an average of 482.

As shown by Molander, Wroblewski and La Due[2,3] the characteristic alterations of serum glutamic oxalacetic transaminase (SGOT) activity have been useful in assessing the presence and the degree of both heart muscle and hepatocellular damage.

Bang, et al[6] reported 39 cases during and after heavy alcohol ingestion and correlated the enzyme activity with blood alcohol levels. 80% of the chronic alcoholics exhibited a significant rise in the SGOT activity after acute alcohol intoxication. In this study it was noted that the enzyme activity remained elevated for from 2 hours to 11 days after the alcohol intake but on the average fell to normal by the fourth day.

As is well known, one of the difficulties in the electrocardiographic interpretation of recent myocardial infarction is the presence of left bundle branch block. Here, the presence of myocardial necrosis raises the enzyme levels of SGOT and can be very helpful in the diagnosis of acute myocardial infarction.

CASE REPORT

A 59 year old white man was admitted to the Delaware Hospital on September 9, 1958 at 5:00 a.m., with the chief complaint of shortness of breath and a rapid heart beat. He had apparently been well until about one week prior to admission, during which time he noticed progressive exertional dyspnea. This became more severe the evening before admission, with sudden increase in heart rate and cold sweat. He did not complain of chest pain but did have a severe constricting type of pain in the epigastrium. The patient had been drinking heavily for many years, apparently with an increase in the amount of alcoholic intake during the week prior to admission; he smoked about 1½ to 2 packs of cigarettes daily.

His past medical history was negative for heart disease or anginal symptoms; however, he had had a subtotal gastrectomy about three years before because of peptic disease, and had also had bilateral inguinal herniorrhaphies. He denied other operations or illnesses.

Physical examination revealed the follow pertinent facts: well developed and well nourished male who appeared apprehensive but oriented, with cold, moist, pale skin without cyanosis. Initial blood pressure was 120/90mm of Hg, temperature 97.4°, pulse 140 and respirations 40. There were minimal sclerotic changes in the eyegrounds. The neck veins were not distended and the thyroid was not palpable. Auscultation revealed crepitant rales in both lung bases posteriorly and sinus tachycardia without murmurs. No friction rub was heard. The abdomen was soft and flat and revealed the scars of previous surgery. Peripheral pulses were adequate and there was no edema; neurological examination was negative.

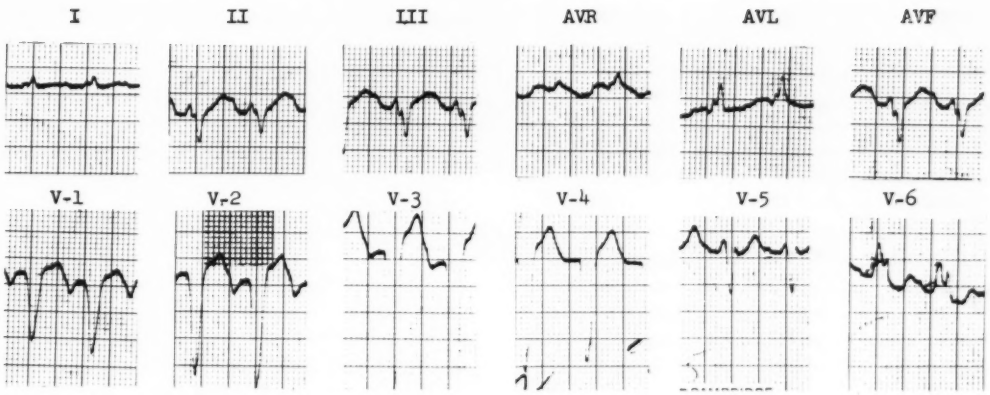
He was placed in an oxygen tent and given sedation prior to special studies.

On the day of admission his electrocardiogram revealed left bundle branch block, first degree heart block and tachycardia. The pattern suggested acute septal infarction despite the presence of the left bundle branch block. A second tracing on the same day revealed ST-T segment changes consistent with an acute process (Fig. 1). On the same day his transaminase was 92 units.

Anticoagulant therapy was begun and rapid digitalization with Cedilanid and digoxin was instituted.

On the second day of his illness his transaminase rose to a level of 410 units in the morning. On the evening of this day, the patient began to show confusion, and was found out of bed. By midnight he was completely disoriented and delirium tremens was obvious. Restraints were required, and by 2:00 a.m. on the third day

FIRST TRACING TAKEN ON 9/9/58



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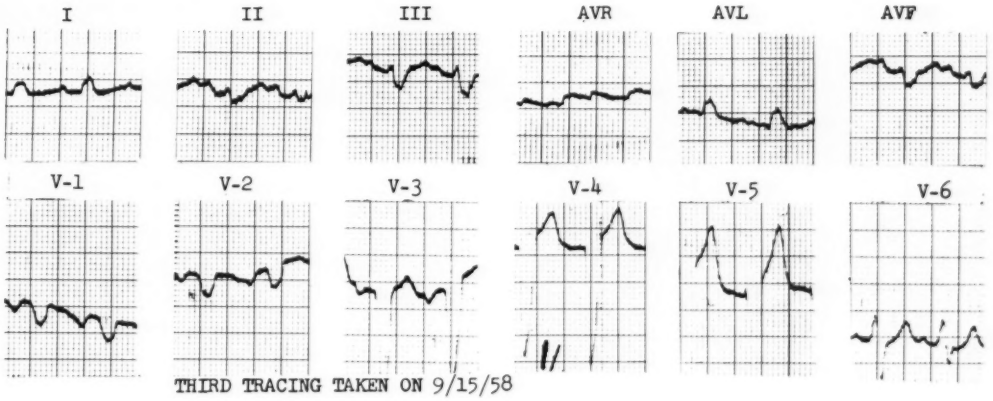

THIRD TRACING TAKEN ON 9/15/58

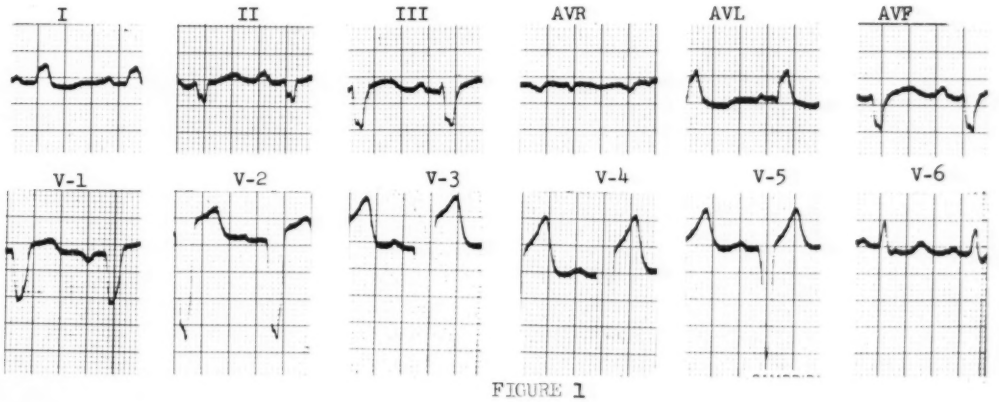

FIGURE 1

he was actively hallucinating and required sodium amytal intravenously plus steroids and pharyngeal aspirations.

He received 300 mgm. of dicumerol on the first day and 200 mgm. on the second. This resulted in a precipitous drop in his prothrombin time to less than 10% where it remained for three days. This, as well as the second rise in transaminase, reflected his hepatocellular injury. Because of small amounts of blood in his throat aspirations and the presence of large hematomata at the site of venous infusions, it was deemed advisable to discontinue anticoagulant therapy. He received 5 mgm. Mephyton intravenously, on the third day of his illness, 10 mgm. the following day, and his prothrombin time returned to 90% of normal on the sixth day. With the use of Thorazine, steroids and symptomatic therapy, the patient's sensorium gradually cleared. On the sixth day the transaminase had dropped to 134 units.

The remainder of his hospital course was uneventful and he was gradually ambulated, being discharged on September 29th.

During the course of his first few days, the following laboratory work was done: hemoglobin 101% (15.8 gm.), WBC 9,000 with 86 polys seg, band forms 2%, lymphocytes 8% and monocytes 4%. VDRL was non-reactive and his initial sedimentation rate was 6mm. Other studies revealed the following: BUN 9 mgm%, feasting blood sugar 96 mgm%, serum cholesterol 246 mgm%, serum sodium 135 meq/1, serum potassium 4.95 meq/1, CO_2 20 meq/1 and chloride 102 meq/1. Urinalysis showed 1+ albumin and was negative for sugar and acetone. On September 17th a portable film of the chest showed the lung fields to be clear and the cardiac shadow to be within normal limits. No free fluid was seen.

DISCUSSION

The value of transaminase in acute myocardial infarction has been particularly useful in the so-called masking forms of this illness. This includes myocardial infarction in the presence of old or recent pericarditis, Wolff-Parkinson-White syndrome, acute infarction superimposed on previous old infarctions, and left bundle branch block. Another potential value of the transaminase level would be in septal perforation after an acute infarction in which a secondary rise in enzyme level would be anticipated. This rise would result from the enzyme release from necrotic septal myocardial cells and also from central lobular necrosis of liver, reported in acute infarction complicated by septal perforation[7].

This case is reported because of the double masking effect of left bundle branch block and acute alcoholic intoxication. The large amounts of enzyme lost from the hepatic cells in acute alcoholism can give a higher transaminase level than myocardial infarction.

The necessity for considering hepatocellular damage in the presence of acute infarction must be considered in the interpretation of transaminase levels.

SUMMARY

Myocardial infarction rarely elevates the SGOT activity above 300 units, whereas acute liver disease may result in a much higher level. In this case, the first rise of transaminase was due, at least in part, to the acute infarction; the secondary rise being due to the additional enzyme released during his delirium tremens. Because of the overlapping of the ranges, the extremely elevated enzyme titers should make one suspicious of additional factors such as liver damage.

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CONGENITAL ABNORMALITY OF THE GALLBLADDER

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A CASE REPORT

Congenital abnormalities of the gallbladder pose a challenging problem to both the radiologist and the surgeon, and even though this condition has been reported with increasing frequency, it still deserves mention in the literature due to its relative rarity and to the difficulies encountered in dealing with it.

According to the classification of abnormalities of the gallbladder presented by Gross in 1936[1] and Flannery and Caster in 1956,[2] the abnormality presented by our patient would be that of the double gallbladder of the "H" or ductular type.

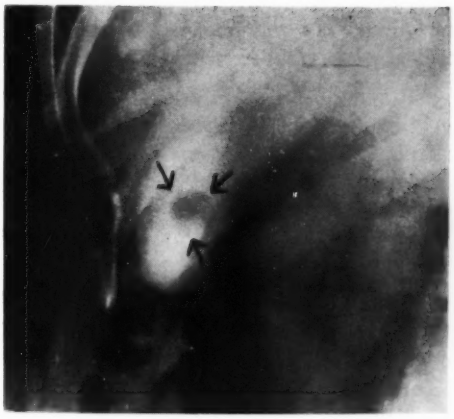

Figure 1

CASE REPORT

This 44 year old white woman was originally seen in 1953 at which time she gave a three year history of indigestion. This indigestion consisted mainly of heartburn, belching of large quantities of gas, abdominal distention and constipation. She stated she had occasional epigastric pain which went through to the right side of her back, but was relatively mild and more noticeable on motion. She had had two attacks of sharp upper right quadrant pain which went through to the back, and these attacks were associated with nausea and vomiting. They were of brief duration and did not require medication. She stated that her only apparent food intolerance was to eggs, and that her symptoms appeared regardless of the type of diet she followed. At the time of her first examination the abdominal findings were negative; no tenderness or masses could be demonstrated. A gastrointestinal x-ray series was normal. She also had had two cholecystograms which showed non-function. A repeat cholecystogram showed the gallbladder to have some function but there was a large calculus present. (See X-ray #1)

She was admitted to the Delaware Hospital on 1/14/54 where she remained until 1/22/54. History of present illness was essentially as given above. Family history was not important. Past history revealed no serious illnesses; she had had the usual

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childhood diseases and tonsillectomy and adenoidectomy in childhood. She had had a D&C in 1941 following a miscarriage and this has been her only pregnancy.

Physical examination at this time was essentially negative except for two unrelated findings: (1) a small lipoma or cyst of the left shoulder, and (2) a mild degree of tenderness in the upper right quadrant of the abdomen. Admission blood count, urinalysis and serology were entirely negative.

A cholecystectomy was done on 1/15/54. The gallbladder was small, thick-walled, chronically inflamed, and the mucosa when opened was granular in appearance. There was one stone 1.5 cm. in diameter. Small fibroids were palpated in the uterus. The appendix was not removed, as the cecum could not be delivered through the incision.

Pathological report showed grossly a gallbladder measuring 4x3 cm.; the wall was fibrotic and the mucosa pale green and granular. There was one pale yellow, translucent calculus measuring 1.5 cm. in diameter. A diagnosis of chronic calculus cholecystitis was made.

The patient made a relatively uneventful postoperative recovery and was discharged to her home on the 8th postoperative day.

She was seen periodically until 2/15/54 at which time the wound was well healed and she appeared to have made a good recovery from her surgery. During the next four years she complained of having frequent attacks of sudden violent discomfort in the upper portion of her scar which appeared without reason and were of short duration, and she felt that there was a bulge in the area. She could give no idea as to what produced this apparent spasm as it appeared to bear no relation to food or activity. Repeated examination disclosed no evidence of any weakness in the scar and no tender points along the scar. The second complaint which persisted through all this time was continuing indigestion. The patient gained about 30 pounds in weight but still was unable to get back to a full general diet. She felt that more foods produced symptoms than had done so prior to her surgery.

In 1957 her history was very suggestive of a peptic ulcer. A gastrointestinal x-ray series done at that time showed no abnormality except for a small diverticulum of the third portion of the duodenum and some evidence of spasm in the prepyloric area. She was given antispasmodic and alkaline tablets and seemed to do reasonably well.

She was readmitted to the Delaware Hospital on 1/14/59 for study, with an admission diagnosis of esophagitis and gastritis. The history at the time of this admission disclosed a two year story of substernal soreness wich seemed to go around the rib cage on both sides anteriorly. This soreness was not related to meals or to exercise, but was noticed to be worse at night, particularly when she was lying on her right side. There was no nausea or vomiting associated with this. The patient felt that she had much more gas and much more food intolerance than she had prior to her previous gallbladder surgery.

Physical examination was not remarkable except for some persistent soreness and spasm in the upper part of the right abdomen.

Laboratory findings on this admission were essentially normal; hemoglobin was 88%, RBC 4,500,000, and WBC was within normal limits. Urinalysis was negative; fasting blood sugar 98 mgm%; serum amylase 190; blood cholesterol 296; bilirubin direct 0.10, and total 0.54, well within normal limits. An upper G.I. x-ray study was done. There was some question whether there was a small peptic ulcer in the esophagus. The diverticulum of the third portion of the duodenum was again noted, as was a very small hiatus hernia. Barium enema was reported negative except for an irritable colon. Chest x-ray was negative. Cholographin study was reported to show a finger-like projection measuring 6x1 cm. in the upper right quadrant, with several rounded shadows present, and a diagnosis of a dilated cystic duct stump with calculi was made. (See X-ray #2). An electrocardiagram was normal.

ANNUAL MEETING

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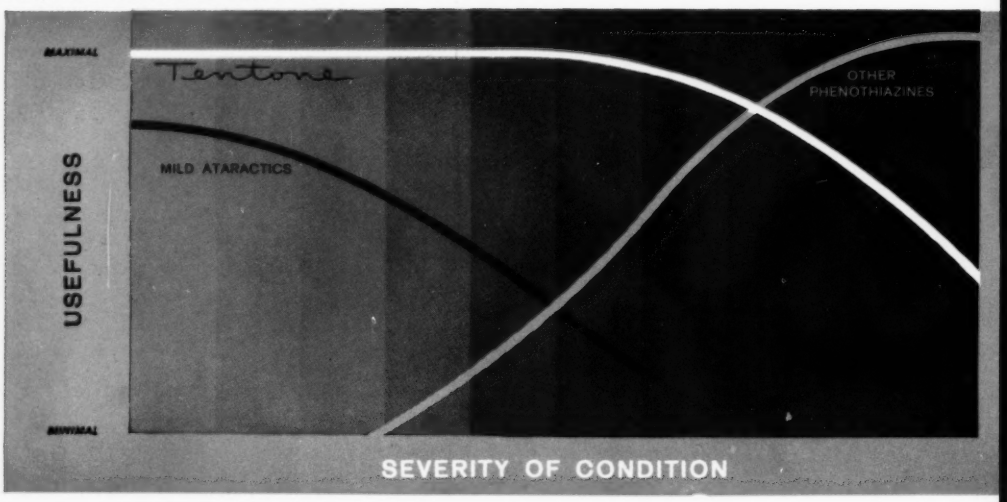

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Figure 2

With a preoperative diagnosis of gallstones and a dilated cystic duct stump, the patient was operated upon on 1/22/59. A long, oblique, subcostal incision was made and the rectus muscle on the right side divided across at about the site of the drainage scar in the previous incision. Massive adhesions were found from the liver edge down to the common duct, and a considerable time was taken in freeing this area. The entire scar of the liver bed of the removed gallgladder was followed down to the common duct area, and no evidence of any dilated cystic duct stump or stones was found. Continuing the dissection posteriorly, all of the adhesions were freed from the liver bed, and the duodenum was freed and retracted medially and downward. With this exposure the common duct was then seen and a cystic duct was found leading from it about 1 cm. below the site of the scar of the previous surgery. This was freed at its attachment to the common duct and then followed laterally for a distance of about 2 cm., when it appeared to go directly posteriorly to the posterior portion of the right lobe of the liver. When this area was exposed a dilated sac containing 5 or 6 green faceted stones was found; this was removed. The common duct was palpated but not opened; other structures in the area were noted to be within normal limits except for the many adhesions about them. A cigarette drain was inserted to the site of the cystic duct stump and the wound closed in layers. The patient left the operating room in good condition. It was felt at the time of the completion of this surgery that we were dealing with a second gallbladder which lay in the posterior portion of the right lobe of the liver, rather than with a dilated cystic duct stump from the previous surgery.

The Pathology Department presented the following report: "Gross: Received in Zenker's solution a somewhat tubular structure measuring 2.2 cm. in length and 0.9 cm. in maximum diameter. On sectioning, the wall has a thickness of 2 mm. and the mucosa averages 1-2 mm. in thickness. Also received are 5 faceted, soft green stone averaging 0.8 cm. in diameter. Microscopic: Sections show a cystic space lined by columnar epithelium forming papillary projections into the lumen. The substantia propria is vascular and moderately infiltrated by chronic inflammatory cells. Muscular coats are thickened and the mucosal glands cut in cross-section are found deep to the muscle layer. The serosal surface is thickened and the vessels have thickened walls. One section shows two broad stalk-like projections into the lumen bordered by columnar cells and containing smooth muscle bundles in the loose connective tissue stroma. These structures are considered to be the spiral valve of Heister located in the neck of the gallbladder and the upper end of the cystic duct. In view of history and operative findings the structure submitted is consistent with chronic cholecysitis and duplicated gallbladder."

The patient's course in the hospital following this surgery was excellent. Drain was removed on the 4th day and the wound has gone on to excellent healing. The patient reports two interesting facts: first, that the sudden attacks of pain which she had in the previous incision have not recurred; the incision feels much more comfortable than it has at any time since her first surgery. Second, she has been able to increase her diet rapidly and food intolerance to this point has been relatively minor. She states that she feels a great deal better than she has at any time in the past six years. She has returned to full activity and is practically back to a full general diet.

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MAN AND HIS FOOD INTAKE

● **The author points out in this article that there is no "weight control" brain center. The Western World as a whole indulges in overeating through hereditary, environmental and psychologic influences. Harnessing will power is the only answer to the regulation of food intake based on energy requirements.**

LEMUEL C. MCGEE, M.D.*

Increasingly, the spotlight of scientific inquiry is placed on nutrition. Emphasis upon variants in fat metabolism has influenced both theory and experimental design in studies of cardiovascular disease. A supply of adequate protein is a well recognized major dietary need for millions of people. One-fourth of the residents of the Western World suffer from an excessive caloric intake. Such observations have led to further explorations on the biologic mechanisms controlling appetite, hunger, satiety and related aspects of why man eats what he eats. The results of the physiologists' probing of these matters is of concern to physicians who must advise patients regarding their day to day dietary habits and needs. Here is an effort to summarize what the physiologist has been up to, what he has noted that is useful to the practitioner.

Hunger has been defined as the disagreeable complex of sensations, including epigastric pangs, which result from a deficit in body nutrients.

Appetite is an affective state usually a pleasant sensation, defined as the desire for food. It has been described as a learned physchological experience.[1]

Satiety is the state of being filled beyond natural desire, in this instance with food.

Since healthy adult men and animals generally tend to maintain constant body weights over extensive periods of time, a physiologic regulation of food intake based on energy requirements has long been supposed. The mechanisms of such regulation are incompletely understood. Since there are marked variations in the day-to-day food intake of man, it is reasonable to assume that what is being regulated is the body's store (excesses or deficits) of nutritional elements.[2]

The nervous system influences food intake in several ways. The complex sensations of satiety, appetite and hunger are mediated by it. Cannon and Carlson demonstrated that gastric "hunger" contractions are cues for eating.[3] The stimulation of oropharyngeal sensory receptors (tasting, chewing and swallowing food) tends to reduce food intake. Gastric distention induces an inhibition of the act of eating through reflexes. The neural role is further evident in the "feeding reflexes" wherein visual, auditory, olfactory, tactile, gustatory and enteroceptive reflexes influence food in-

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take. Clearly appetite and its consequence of eating is swayed by factors varying from pleasant odors to subtile seduction by the television screen. A psychiatric hypothesis is that much hyperphagia in humans is to serve emotional needs rather than nutritional demands.[1] Lesions in the ventromedial nucleus of the hypothalamus in animals bring about an increased food intake. Lesions in the lateral area at this level of the hypothalamus diminish food intake.

Brobeck[4] observes that while there is no "weight control" brain center as such, weight is controlled indirectly by at least three mechanisms which are under physiologic direction: food intake, heat loss, and exercise. There is evidence that heat and certain metabolites influence food intake through the central nervous system. Metabolic influences on eating presumably act through the hypothalamus (inhibitory effects mediated by the ventromedial area). Hypoglycemia is associated with increased food intake. The role of glucose metabolism is further emphasized by the recent observation that glucagon (a pancreatic glycogenolytic factor) given parenterally diminishes hunger sensations, gastric contractions and food intake in human subjects.

Mayer[5] has presented a "glucostatic" hypothesis which assumes that the rate of passage of glucose (or of ions associated with its transfer to cells) into "gluco-recep tors" of the ventromedial hypothalamus affects feeding behavior. In support of this theory he and others studied differences in the glucose levels of arterial and venous blood (designated as Δ-glucose). Small Δ-glucose values were associated with hunger and hunger contractions, large Δ-glucose values were accompanied by the absence of evidence of hunger. The "glucostatic" hypothesis, while having attractive features, faces conflicting evidence.[3] Some investigators find a poor correlation between gastric hunger contractions and blood glucose levels. Janowitz and Ivy[6] reported that the hunger sensations in human subjects were unaltered by intravenous injection of glucose. Similarly in animals, glucose infusion to create hyperglycemia failed to depress food consumption.

That a genetic factor may dictate a persistent level of food consumption which exceeds the energy output is suggested by the identification of a strain of mice which are congenially prone to hyperglyceria and obesity. For these mice, inactivity plays a large role in their caloric surplus. This finding is of interest in considering the fact that in both adult man and animals living under reduced physical activity the regulation of food intake clearly tends to become less precise, as compared to its precision under living conditions requiring higher energy output by the subjects. Simply stated, as man reduces his activity, his appetite does not decrease in proportion to his actual caloric needs! A group of industrial workers whose physical activity was moderate were found to eat less than did excessively active or exceptionally inactive workers.

One must recognize that the regulatory mechanisms serving the majority of adult men and women can be negated by hereditary, environmental and psychologic influences. When both parents are obese, about 80 per cent of their children will have this trait. Psychologic sway is impressive in the abnormal hyperorexia associated with extreme obesity and the refusal of food in anorexia nervosa leading to marked cachexia. To the extent that the clinician can identify and control the various negating factors, will he succeed in the long term management of proper nutrition of his patients. While accepting a variety of influences on the desire to eat, the fact remains that food-taking is a motor act of skeletal muscles—volunary muscles which are under the control of the will. Harnessing will-power remains the point of breakthrough in dietary therapy.

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STAPHYLOCOCCAL SEPTICEMIA

A REVIEW OF 30 CASES

● **The high mortality rate of staphylococcal septicemia will be lowered only when the medical profession assumes a proper awareness of the problem. Cessation of indiscriminate antibiotic therapy is the most important factor in its prevention. Isolation of the infected patient with scrupulous aseptic and antiseptic practices should be routine.**

W. J. HOLLOWAY, M.D.*
AND E. G. SCOTT, M.T.**

In previous issues of this journal, 1-4, the authors have reported on the epidemiology, susceptibility to antibotics and treatment of infections due to staphylococci. Because of the high mortality of staphylococcal septicemia, even with newer methods of therapy, the authors believe that any experience in the treatment of this disease is worth recording, and offer their own recent experiences at the Delaware Hospital as a case in point.

At the Delaware Hospital during the period between 1950 and 1955, twelve cases of staphylococcal septicemia were reported[3] with a 50 per cent mortality rate. In the three subsequent years (1956, 1957, 1958), thirty patients suffering 32 episodes of septicemia due to coagulase-positive *Staphylococcus aureus* have been studied at this hospital. Obviously, there has been a significant increase in the number of cases of septicemia during this period, which does not necessarily reflect an increase in the virulence or infectivity of the local strains of staphylococci. In fact, there has *not* been a significant increase in the number of patients admitted to the hospital with staphylococcal blood stream infection. Subsequent figures will demonstrate that the major increase has been in *nosocomial infections*, sixty per cent of the cases being considered "hospital infections."

All of the patients included in this study were indisputable cases of septicemia; and suspected case of transient bacteremia was not included. All 32 episodes were characterized by acute illness in association with a positive blood culture. In 40 per cent of the cases, the blood culture was positive more than one time. Of two patients studied in 1956, each suffered two bouts of staphylococcal septicemia, separated by at least seven months. One patient also experienced a gram-negative rod septicemia in the interim. Also in this study are four children with staphylococcal septicemia associated with acute osteomyelitis. In these cases the organisms isolated were antibiotic—sensitive and the results of treatment were uniformly good. For the sake of completeness they have been included in this study. However, since this is a different disease with generally favorable outcome, a corrected mortality rate has been applied, by excluding these four cases in the calculation.

Table I lists the number of cases per year and also indicates the number of nosocomial infections. In 1956, fifteen episodes (13 pts.) of septicemia resulted in four deaths. Excluding the four children with

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TABLE I

STAPHYLOCOCCUS SEPTICEMIA — 1956-1958

YEAR	HOSPITAL INFECTION	NO. HOSPITAL INFECTION	TOTAL	DEATHS	MORTALITY* PER CENT
1956	7	8	15 (13 pts.)	4	36.4
1957	5	2	7	2	33.3
1958	8	2	10	7	70.0
TOTAI 3 YEAR PERIOD	20	12	32 (30 pts.)	13	48.2

*CORRECTED — LESS CASES OF ACUTE OSTEOMYELITIS — SEE TEXT

acute osteomyelitis, the corrected mortality is 36.4 per cent. In 1957, only seven cases of septicemia occurred, with a corrected mortality of 33.3 per cent. The final year of the study reveals an alarming increase in mortality—70 per cent—which represents seven deaths in ten patients. This increase in mortality appears to be related to the increase in nosocomial infections in the Delaware Hospital during 1958. In this three year period, 20 patients probably acquired staphylococcal infection and subsequent septicemia from the hospital environment. Eleven of these patients died, a mortality rate of 55 per cent. Twelve patients were admitted to the hospital with staphylococcal blood stream infection, and of these, two died (16.6 per cent mortality). It is of interest that both patients who died of infecion apparently acquired outside of the hospital environment were shown at autopsy to have staphylococcal endocarditis, a disease which has an exceptionally high mortality.[5] The corrected mortality for the three period of this survey (48.2 per cent) is essentially unchanged from that of the previous five years (50 per cent). However, the 70 per cent mortality in 1958 is the highest we have experienced.

The thirty patients included in this study study ranged in age from 7 months to 84 years. All but two of the children with septicemia had acute osteomyelitis. One, a seven month old child, died with staphylococcal pneumonia complicating a tracheotomy. Staphylococcal septicemia with acute lymphoma was fatal to a 15 year old boy. A 39 year old man with psoriatic arthritis died of staphylococcal endocarditis. Of the remaining ten fatalities, all were over 50 years of age and nine were over 70 years of age. Staphylococcal septicemia obviously carries a high mortality in the older age groups; in fact, there were only two patients over the age of 50 among the survivors.

Table II lists the underlying or contributing factors present in these 30 patients with staphylococcal septicemia. From the total number of ancillary problems, it can be seen that some patients had more than one complication, which did not, of themselves, increase the mortality. Operative reduction of a fractured hip was the surgical procedure most frequently complicated by a staphylococcal septicemia, and this

TABLE II

STAPHYLOCOCCAL SEPTICEMIA

UNDERLYING AND CONTRIBUTING FACTORS — 30 PATIENTS

DISEASE	NO. OF PATIENTS	DISEASE	NO. OF PATIENTS
Wound infection	6	Paraplegia	2
Acute osteomyelitis	6	Pyarthrosis	2
Steroid therapy	5	Diabetes mellitus	2
Fractured hip	4	Dermatitis	2
Decubitis ulcer	3	Thyrotoxicosis	2
Furunculosis	3	Lymphoma	1
Endocarditis	3	Leukemia	1
Pnuemonia	3		

group suffered a high mortality rate. The age of the patient undergoing hip surgery accounts for this grave prognosis, all of these patients being over 70 years. On the contrary, acute osteomyelitis with staphylococcal septicemia carried a good prognosis, primarily because of the young age group involved. Three of the six patients with septicemia complicating postoperative wound infection did well, because the infection was amenable to incision and drainage. The three in whom surgical drainage was not carried out ended fatally, despite heroic antibiotic therapy. It is known that patients receiving sterioid therapy are unusually susceptible to infections caused by staphylococci. It has been reported that cessation or reduction of steroid therapy is sometimes necessary to effect a cure of the bacterial infection.[6] Three of the five patients in this group died while receiving steroid therapy; however, the disease being treated with sterioid therapy could be expected to result in a fatal outcome.

It is apparent that patients with chronic illnesses who are exposed to a hospital environment for any length of time are good candidates for acquiring infections due to antibiotic-resistant hospital strains of virulent staphylococci. The lowered resistance associated with steroid therapy, metabolic diseases, blood dyscrasias, immobility, poor respiratory exchange and extensive dermatitis, contributes in the initiation of this nosocomial infection.

LABORATORY DATA

All of the patients reported in this study had at least a single isolation of a coagulase-positive *Staphylococcus aureus* from the blood stream. In 19 patients a similar organism was also isolated from another site. These organisms were identified colonially on blood agar and morphologically by gram-stain. Sensitivity tests were performed by the disc plate technique, and in a number of cases by the test-tube dilution method. Our experience with this microorganism has indicated that there is a consistent correlation between disc and test tube sensitivities. Bacteriotphage typing was not available at the time of this study.

Table III shows the antibiotic susceptibility pattern of the organisms isolated. It will be noted that the hospital strains most frequently recovered were resistant to penicillin, tetracycline and, in eight instances, to erythromycin. The organisms isolated

TABLE III

STAPHYLOCOCCAL SEPTICEMIA
ANTIBIOTIC SUSCEPTIBILITY OF STAPHYLOCOCCI (DISC TECHNIQUE*)

Organisms from Hospital Infections		Organisms from Non-Hospital Infections
3	Sensitive All antibiotics	4
1	Penicillin Resistant	5
6	Penicillin, Tetracycline — Resistant	3
8	Penicillin, Tetracycline, Erthyromycin — Resistant	
1	Penicillin, Tetracycline, Chloramphenicol — Resistant	
1	Penicillin, Tetracycline, Erythromycin, Chloramphenicol — Resistant	
20	TOTAL	12

*Penicillin — 2 units
Tetracycline — 5 mgm
Erythromycin — 2 mgm
Chloramphenicol — 5 mgm

from the 12 cases already infected on admission showed a lower order of resistance.

Leukocytosis was a consistent finding in these patients. The initial count in 31 episodes of staphylococcal septicemia was above ten thousand in 30 instances, twenty to thirty thousand in seven patients and over thirty thousand were patients. All of the differential counts showed a marked shift to the left. The leukocyte count of the patient with leukemia is not included for obvious reasons.

Five of the 13 fatalities were uremic during the course of illness. In three of these, there was urinary tract disease sufficient to account for the azotemia. In the remaining two, staphylococcal renal abscesses were suspected clinically and found to be present at post mortem examination. Urinalyses were frequently abnormal in these critically ill patients, but could not be correlated with specific renal damage by the staphylococcus. Anemia was a common finding, resulting from the septicemia or the severe underlying disease.

TREATMENT

The results of therapy of staphylococcal infections are difficult to evaluate. This is particularly true when considering infections of the skin, wounds and other superficial tissues. Staphylococcal septicemia allows a more accurate assessment of ther-

TABLE IV

STAPHYLOCOCCAL SEPTICEMIA — RESULTS OF THERAPY

	Good	Poor	Indeterminate
Penicillin	1	4	2
Chloramphenicol	3	5	—
Tetracycline	—	6	—
Novobiocin	1	1	—
Neomycin	3	—	—
Vancomycin	3	—	—
Kanamycin	—	—	1
Ristocetin	—	1	—
Penicillin and Streptomycin	—	3	—
Penicillin and Chloramphenicol	2	—	—

apy, because one can be more certain of the significance of organisms isolated from the blood stream. In tabulating the outcome of treatment we have used the classification *good, poor* and *indeterminate*. This last grouping is necessary because it was impossible to determine the effectiveness of the antibiotic course in a few instances.

A number of physicians were responsible for the care of these patients, accounting for the variety of antibiotic regimens. Twenty different antibiotics or combinations were used in 53 courses of therapy. Unfortunately, this diminishes the value of the study as far as evaluation of antibiotics is concerned. As a result of the incidence of nosocomial infections, the Hospital Committee on Infections has become interested in the treatment of patients with severe staphylococcal infections and established

TABLE V

RESULTS OF THERAPY — CONTINUED

	Good	Poor	Indeterminate
Penicillin and Novobiocin	1	—	—
Penicillin and Sulfonamides	—	1	—
Penicillin and Tetracyclines	—	1	—
Chloramphenicol and Novobiocin	2	4	—
Chloramphenicol and Erythromycin	2	—	1
Chloramphenicol and Tetracycline	—	—	1
Erythromycin and Sulfonamides	—	1	—
Pen and Tetra and Sulfa	—	1	—
Pen and Chloro and Strep	—	1	—
Pen and Sulfa and Tetra and Strep	—	—	1
TOTAL	18	29	6

standards of therapy which should aid in assessing treatment results in the future.

A *good* result is defined as clinical improvement in the patient (suggesting eradication of the blood stream infection), frequently, but not necessarily confirmed by negative blood culture. Several of the patients initially considered as *good* results, subsequently relapsed and died. Conversely, a number of the patients with *poor* results were eventually treated with a different antibiotic (or combination), with recovery. Tables IV and V indicate that from 53 courses of therapy, *good* results were obtained 18 times, *poor* results 29 times and *indeterminate* results in six instances. The correlation between the *in vitro* sensitivity of the organism and the *in vivo* response to the antibiotic was excellent. In all of the 18 *good* responses, the organism was sensitive to the antibiotic used. As might be expected, a number of failures occurred when an antibiotic considered to be appropriate was given, but where the severity of illness, poor resistance of the patient and improper dosage or route of administration mitigated against a successful outcome. It should be mentioned that in five cases of septicemia in which antibiotics had failed, cures were effected by surgical drainage of amenable foci of infection. This therapeutic maneuver should certainly not be overlooked.

DISCUSSION

The treatment of staphylococcal septicemia in this hospital needs immediate reevaluation. The increasing incidence of nosocomial infections has increased the number of septicemias due to antibiotic-resistant organisms and a higher mortality has resulted from these infections. Consequently, when septicemia due to a staphylococcus is suspected in a hospitalized patient, therapy should be instituted immediately. Intravenous vancomycin should be given in doses of 1-2 grams per day; if the intravenous route is not feasible, then neomycin or kanamycin may be given intramuscularly. Both of the latter drugs are toxic to the eighth nerve and should not be used in the presence of impaired renal function, unless the renal damage is of itself a result of the staphylococcus infection. Chloramphenicol and novobiocin should not be used individually in the treatment of staphylococcal septicemia. When used together, or singly in combination with erythromycin, good therapeutic results may be expected. However, our experience with these essentially bacteriostatic agents in the treatment of severe staphylococcal infection has been disappointing. It should be emphasized that if an organism is susceptible to penicillin, this drug is certainly the antibiotic of choice.

A more indirect but perhaps more promising approach to the control of staphylococcal septicemia is through the control of nosocomial infections. The important measures of a staphylococcus control program are as follows:

1. Isolation of the infected patient.
2. Protection of the highly susceptible patient.
3. Scrupulous aseptic and antiseptic practices.
4. Cessation of indiscriminate and prophylactic antibiotic therapy.
5. Awareness of the problem by the medical profession.

These measures combined with prompt and adequate treatment of the infected patient should bring about a reduction in mortality from staphylococcal septicemia.

SUMMARY

A clinical review of 32 episodes of staphylococcal septicemia in 30 patients observed over the past three years is presented. The results of treatment are tabulated and some general statements are made concerning the control and treatment of severe staphylococcal infection.

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MASSIVE EXTRAMEDULLARY MYELOMATOSIS OF THE LIVER:

A CASE REPORT WITH REVIEW OF PATHOLOGICAL FINDINGS

KENNETH W. EHRHART, M.D.*

The first authentic report of extramedullary plasma cell lesions associated with multiple myeloma appeared in 1892, according to Hayes[1]. Sporadic reports of such lesions continued to appear in the literature, but in general, extra-osseous manifestations of the disease were considered to be of rare occurrence, except by direct extension from involved bone. Up to the end of 1952 Hayes et al[1] were able to gather 182 cases from the world literature. Their tabulations revealed instances of myelomatosis in practically every organ and region of the body. By far the greatest number of lesions were found in the liver, spleen and lymph nodes, with less frequent occurrences in the kidney, heart and lung. These same authors studied in detail 38 autopsied cases of multiple myeloma at the Mayo Clinic. Their findings, plus the earlier results of a similar study at the Mt. Sinai Hospital in New York[2], indicated that extra-osseous myelomatosis was the rule rather than the exception in multiple myeloma. Both groups reported extramedullary lesions in approximately 70% of the cases studied. The present case is reported because of the extensiveness of the liver involvment.

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CASE REPORT

A 56 year old white woman was admitted to the Delaware Hospital March 20, 1959 in an unconscious state. Past history, obtained from relatives, revealed that she had sought treatment for obesity from many physicians through the years. Her weight usually averaged 250 to 260 pounds but recently there had been a spontaneous loss of 20 to 30 pounds. For approximately five years she had complained of shortness of breath, tiredness and joint pains described as "rotating" in type. Three days before admission she was treated by a physician for epistaxis which had occurred for the first time. At this time she also complained of increased joint pains and an undescribed type of pain in the region of the heart. Following treatment she was advised to remain

at bed rest. The day before admission epistaxis recurred and at this time nasal packing was required to control the bleeding. She was able to move all extremities well, obey commands and take food normally. It was thought, however, that she was slightly incoherent in her conversation. On the day of admission she was found to be incontinent of urine and semi-stuporous. By the time of admission the latter state had progressed to one of deep unconsciousness.

Physical examination: Respirations were 26 per minute and labored, BP 140/90, Pulse 104-150 per minute and regular. The pupils were dilated and responded minimally to light. Bilateral papilledema and slight retinal hemorrhages and exudate were noted on funduscopic examination. The deep reflexes were generally hypoactive and the corneal reflex was reported as slight to absent. A spinal puncture revealed an opening pressure of 370 mm. of water; the closing pressure was 350 mm. The tap was thought to be slightly traumatic. Several large ecchymotic areas were present in the abdominal region measuring 10-15 cm. in diameter. Smaller ecchymotic areas were located on the extremities but only a few petechiae. The Rumple-Leede test was negative.

Laboratory studies: Hemoglobin 8.5 gm%; RBC 2.7 M; reticulocytes 1.2%, WBC 11,200; polys 71%, bands 16, lymphs 9, monocytes 3; capillary platelets 150,000. Urinalysis: sp. gr. 1.012, albumin 1+, sugar negative, acetone 2+, RBC 4-6/hpf, WBC 4-8/hpf. BUN 32 mgm.%, CO_2 7 millimoles/liter; prothrombin time 23% of normal. Spinal fluid: 7 WBC/cumm, moderate number of RBC's, Pandy 1+.

Hospital course: The patient was seen by neurosurgical and hematological consultants, but expired within four hours before any definite treatment was started. A supravital preparation of finger blood by the hematologist showed marked rouleaux formation. Occasional normblasts and plasma cells were seen. The bleeding tendency was thought to be due to a mixed deficiency of clotting factors. Clinically, a diagnosis of cerebrovascular accident was made.

Post mortem examination: The autopsy was performed approximately 14 hours after death. Significant findings included the ecchymotic areas previously described. The nares and oropharynx contained dried blood. There was 300 cc. of grossly bloody fluid in the stomach. The mucosa was intact. The myocardium of the interventricular septum appeared grossly to be deeply congested but on section there was actual interstitial hemorrhage. The heart was enlarged to 550 grams and the coronary vessels were moderately sclerotic. Although there was no evidence of injury to the scalp or skull, a subdural hematoma was present in the right parietal area. The brain weighed 1400 grams and appeared edematous and congested. The cortex underlying the hematoma was slightly depressed. The lungs showed congestion and edema. The kidneys were slightly swollen and appeared pale. Examination of the vertebral bodies revealed no evidence of tumor formation. The bony structure was somewhat osteoporotic and the marrow more pale than usual. Marrow smears were made.

The liver was markedly enlarged, extending 11 cm. below the right costal margin, 14 cm. below the xyphoid process and 8 cm. below the left costal margin. It measured 38x12 cm. and weighed 5300 grams (the largest liver in the articles reviewed weighed 3300 grams). The parenchyma had a mottled red-yellow appearance with almost complete loss of the usual lobular markings. Scattered throughout the parenchyma were dark brownish-black nodules measuring up to 5-10 mm. in diameter. The spleen weighed 550 grams, was firm, had a relatively dry pulp and contained no visible follicles.

Microscopic findings: The normal architecture of the liver was diffusely altered due to massive infiltration of the sinusoids by foreign cells, many of which appeared to be well-differentiated plasma cells. Every lobule was infiltrated. (Fig. 1) The infiltrate extended from the portal area to the central veins. The sinusoids were so distended by the foreign cells that practically every liver cord was compressed to some

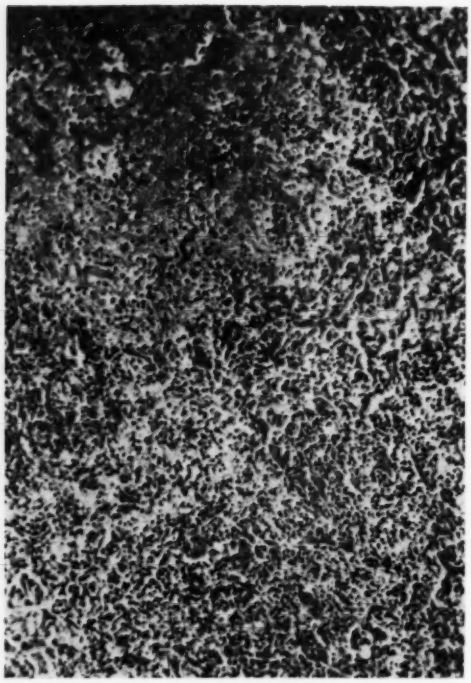

Fig. 1. Typically infiltrated liver parenchyma. Area destruction left upper corner. 75X H&E

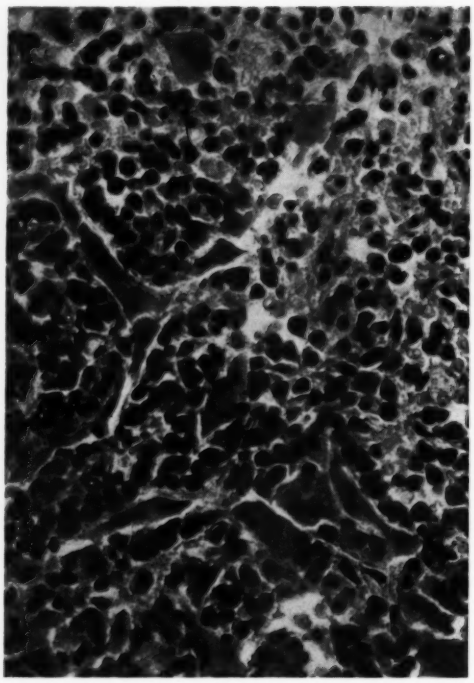

Fig. 2. Myeloma cells densely infiltrating liver sinusoids. Trichrome stain. 325X

degree. (Fig. 2 and 3) Most lobules contained areas of extreme liver cell atrophy and foci where the liver cells had been completely replaced by the myelomatous cells. The dark nodules seen grossly proved to be true plasmacytomas, being composed purely of neoplastic plasma cells. The central portions of these nodules were hemorrhagic, probably accounting for their dark appearance grossly.

The cells in the sinusoids appeared to lie free in the lumina. (Fig. 4) In the less densely involved sinusoids the cells had an abundant eosinophilic cytoplasm without vacuoles or granules. The nucleus was usually round, eccentrically located and contained prominent chromatin clumps located peripherally. This type of cell was also seen in the nodules. However, in the nodules there was definite pleomorphism. Cells varied in size and multinucleated forms containing 2-8 nuclei were rather frequent. (Fig. 5) Mitoses were rare but individual bizarre cells were seen.

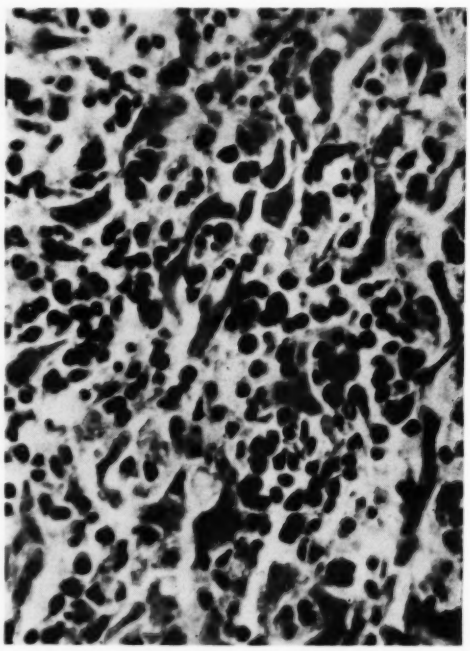

Fig. 3. Portion of liver lobule showing atrophy and separation of liver cells. H&E 325X

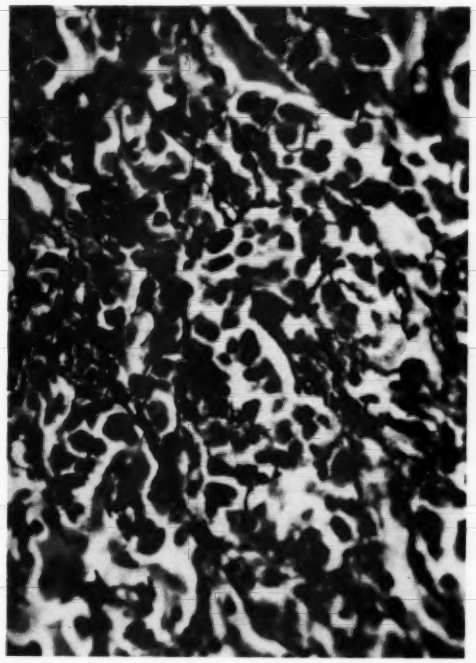

Fig. 4. Liver sinusoids. Myeloma cells free in the lumina. Reticulin stain. 325X

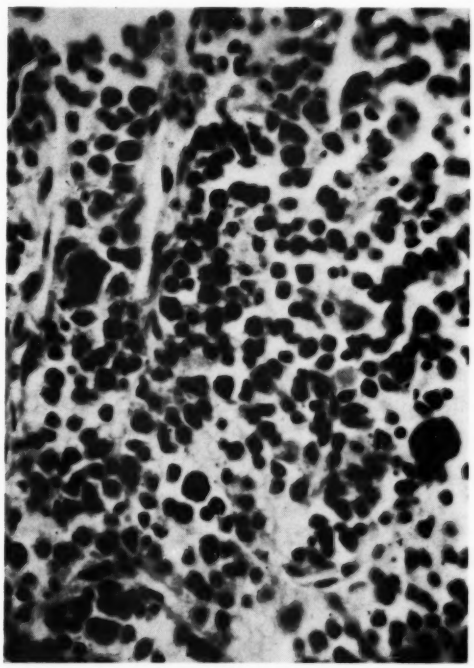

Fig. 5. Myelomatous nodule, liver. Note variation in cell size and multi-nucleated forms. H&E 325X

The splenic parenchyma was almost totally replaced by cells similar to those described in the liver. There were no normal lymphoid follicles. The only remaining lymphocytes were present as cuffs about some of the arterioles.

The bone marrow smears made at the time of the autopsy were disappointing. Due to the extreme post mortem changes, it was impossible to do differential cell counts. One received the general impression that the smear was consistent with a leukosis and that some of the cells resembled plasma cells; but that was as much as could be determined.

DISCUSSION

The immediate cause of death was attributed to the subdural hematoma and cerebral edema. Because of the patient's rapid exodus there is little clinical information to correlate with the post mortem findings. In view of the diffuse myelomatosis of the liver and spleen, multiple myeloma is the most likely diagnosis. Hemorrhagic phenomena are relatively common in this disease, particularly in the terminal stages[6]. The tendency for marked rouleaux formation to occur is also frequently cited as a possible clue to the disease. The presence of a few plasma cells in the peripheral blood, possibly insignificant by itself, is of importance considering the myelomatosis found in the viscera. The low prothrombin time is readily explained by the extensive damage to the liver and no doubt contributed to the bleeding tendency. Also, a low reticulocyte count with a moderately severe anemia is consistent with a marrow unable to respond because of replacement by myeloma. The fact that tumor nodules were not seen grossly in the vertebral bones does not make the diagnosis of multiple myeloma less tenable, for it is well documented that the disease may occur as a diffuse myelomatosis in the marrow. It is in such cases that extensive myelomatosis of the viscera is most likely to be present[5].

CRITERIA FOR THE DIAGNOSIS OF EXTRAMEDULLARY MYELOMATOSIS

The diagnosis of extramedullary myelo-

matosis depends on searching for, and finding, collections of identifiable myeloma cells. Myeloma cells are considered to be abnormal or immature plasma cells. Most of the recent writers on the subject believe that these cells probably originate from reticulum cells[5]. Typically, in tissue sections, myeloma cells are larger than plasma cells. They have an abundant cytoplasm which is usually eosinophilic, but which may be slightly basophilic. The more immature forms may contain vacuoles. In well differentiated cells the nucleus is eccentric and has coarse peripheral clumps of chromatin, as does the normal plasma cell. Immature cells may have the nucleus located centrally and have either a coarse or a fine chromatin pattern. Both types of nuclei contain a nucleolus which is often very large. Cells with the fine chromatin pattern and a large nucleolus may closely resemble reticulum cells[5]. A small cell variant of the myeloma cell has been described[2]. This cell is about half the size of the usual myeloma cell, has a scanty cytoplasm and resembles a lymphocyte. Its nuclear characteristics, however, are similar to the larger cell. The large cell type is usually the predominant abnormal cell in extramedullary lesions; but both cell types are often present in the same lesion and occasionally the small cell type is the predominant one. In most lesions cells identical with normal plasma cells are also seen. Multinucleated cells are usually present, particularly in the nodules. They commonly contain 3 to 4 nuclei but numbers up to 20 have been described. Mitotic figures are not numerous in the usual case but may be numerous in unusually malignant forms of the disease.

When the visceral involvement is extensive, as in the case presented, there is no difficulty in making the diagnosis. With minimal lesions the difficulty may be considerable. This has been cited as one reason the diagnosis of myelomatosis has not been made more frequently in the past[2]. Small collections of myeloma cells have to be differentiated from collections of normal plasma cells which may be present in the tissues in response to various inflammatory processes. Collections of plasma cells have also been described in the lymph nodes and in associateion with malignant tumors. Also adding to the difficulty of differentiating normal from abnormal cells is the fact that post mortem changes and poor fixation often obscure the finer cytological details. When this happens, special stains such as Giemsa's and methyl-green-pyronin may be used to aid in demonstrating nucleoli. By comparing the visceral cells with myelomatous cells in the marrow, similarities may become apparent which enable their establishment as myeloma cells. This is a valid method, since the marrow cells undergo the same postmortem changes.

PATTERN OF VISCERAL INVOLVEMENT

TABLE I

INCIDENCE OF ORGAN INVOLVEMENT*

Organ	Incidence in 68 cases	Percentage
Spleen	41	60
Lymph nodes	32	50
Liver	24	35
Kidneys	5	7
Lung	3	5
Other organs	Each less than 3	Each less than 2%

*Compiled from references 1 and 2.

Table I shows the frequency with which the various organs were involved in the two reports previously mentioned[1,2]. In over half the cases more than one organ was involved. The myelomatous lesions were concentrated in organs which are a part of the extramedullary hemapoietic system. In many instances the liver, spleen and lymph nodes were simultaneously involved, though not necessarily to the same degree. The lymph nodes and spleen frequently were infiltrated when the liver was not involved. The liver was never the only organ involved[2]. Most of the positive lymph nodes were obtained from the various retro-peritoneal chains, but as a rule cervical and auxillary nodes were not available for examination. In general, the incidence of positive nodes was found to be directly proportional to the number of nodes examined.

GROSS PATHOLOGY

There is a tendency for the extramedullary lesion to form nodules (plasmacytomas) similar to those found in the bone marrow[4]. Such nodules may be seen grossly in the liver and occasionally in the spleen. Although usually multiple, sometimes there is only a single visceral plasmacytoma. The nodules vary in size from 1 mm. to 2mm. up to 10 mm. in diameter, are gray or white and have a firm consistency. More often the plasmacytomas are not of sufficient size to be visible grossly. In the absence of gross nodules, irregular grayish streaking with obscurity of the lobular architecture is sometimes seen in the liver. The usual myelomatous liver is of normal weight or only moderately enlarged. The largest liver reported in the review articles weighed 3300 grams[2].

Enlargement of the spleen was a common finding with myelomatosis of that organ. All spleens over 500 grams were diffusely infiltrated. Some moderately enlarged spleens, however, were not involved, while others or normal weight were[2]. More significant than enlargement was the presence of a homogeneous cut surface, grayish areas, increased consistency and loss of follicular markings. Myelomatosis of the spleen was more often of a diffuse type[4]. Gross nodules were not commonly seen.

Positive lymph nodes were usually moderately enlarged. The larger nodes were described as fleshy, and extensively involved nodes bore some resemblance to the nodes seen in lymphomas. The nodes were usually discrete and firm. Entirely normal-appearing nodes were occasionally positive for myeloma cells.

Although the preceding gross signs of myelomatosis are helpful when present, it should be emphasized that in approximately 50% of the cases there were no gross changes suggesting that the viscera were involved.

MICROSCOPIC PATHOLOGY

The most common finding in the liver was the presence of myeloma cells in the sinusoids. These were most often concentrated in the mid-zone or in the central portion of the liver lobules, a distribution similar to that seen in myelogenous leukemia. With more advanced disease, the sinusoids become distended and myelomatous nodules are formed. Occasionally, the infiltrate is limited to the periportal areas. The microscopic pattern in the lymph nodes and spleen are somewhat similar. When the lesions are minimal, myeloma cells appear in the medullary portion of the nodes or in the sinusoids of the spleen while the remainder of the organ retains its normal lymphoid structure. With progression of the disease, changes from partial to complete replacement of the parenchyma occur. The microscopic features of myeloma cells were described previously.

PATHOGNESIS OF MYELOMATOSIS

Recent authors favor the theory that extramedullary lesions develop primarily in the visceral organs from reticulum cells located in them. Advocates of this concept maintain that multiple myeloma is a generalized disease of the entire hemapoietic system and not only the intramedullary portion[7]. Potential cells in the viscera may be stimulated to produce myeloma cells by the same stimulus that produces them in the marrow.

ACKNOWLEDGMENTS

We wish to thank Drs. Edward A. Gall of the University of Cincinnati, I. N. Dubin of Women's Medical College of Pennsylvania, R. Philip Custer, Presbyterian Hospital, Philadelphia, and the Armed Forces Institute of Pathology for their help and interest in reviewing slides from this case. All confirmed the diagnosis.

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IN BRIEF . . .

Awards

The Department of Physical Medicine and Rehabilitation of the Eugene du Pont Memorial Hospital, Wilmington, is the recipient of a $9,500 grant awarded by the Easter Seal Research Foundation toward research for perfecting a lightweight mechanical hand to assist persons crippled by paralysis. Chief investigator is Arthur J. Heather, M.D., medical director of the Department of Physical Medicine and Rehabilitation, who has already developed a model of the improved hand to increase the number of activities a person with hand paralysis can manage unassisted. According to Dr. Heather, the hand is hydraulically operated. By using it, a patient can shave, feed himself, use the telephone, write and carry out numerous activities that otherwise would be impossible. The Easter Seal Research Foundation grant will support research for nine months to perfect the present model and build three additional models for field test purposes.

Dr. Heather reports that another recent grant of $8100 has also been awarded his department by the Delaware Heart Association for the development of an impedance plethysmograph to measure blood flow by changes in electrical resistance of the skin. The Department of Physical Medicine and Rehabilitation has already built a prototype which it has been using on patients in connection with its work with the space research laboratory.

New High

Open Doors, in their annual survey on foreign physicians, showed a new high of 8,392 doctors from 91 countries in training here this year —an increase of 10% over last year and 65% over five years ago. The Far East again sent the largest number, with the Middle East showing the greatest increase—25% more doctors than last year.

New Low

The 17½% reduction in the price of Lysine Monohydrochloride announced by Merck & Co. proves what is possible in the drug field when the research and marketing are paid for. As this is their second reduction in 6 months, this brings the total to 37.5%.

Noises

Dr. Lemuel C. McGee of Wilmington was quoted in *Industrial Medicine and Surgery*, on the decibel value and frequency ranges of noises which affect the hearing. In his address to the Congress of Industrial Health recently, he stated that big city noises such as trucks, buses and air hammers carry no threat and that the only noise that might seriously affect the ears is a high-frequency kind made by metal rubbing on metal at from 90 to 110 decibels.

Dr. McGee, Medical Director of the Hercules Powder Co., was recently presented with the Knudsen Award at the Annual Meeting of the Industrial Association in Chicago, for his outstanding contribution in the field of industrial medicine. The Knudsen Award was established to increase the recognition of the importance of medical programs in industry and to promote the human touch in the medical care of workers.

PRESIDENT'S PAGE

A. R. SHANDS, JR., M.D.

President,
Medical Society
of Delaware

With the acceptance of Dr. Dean W. Roberts to an invitation to participate in the 1959 Annual Meeting's Seminar on Aging, the scientific part of the program is completed. We are most fortunate in being able to have an unusually able and well qualified panel of speakers. In addition to Dr. Roberts, Past Executive Director of the Joint Committee on the Aged and now Executive Director of The National Society for Crippled Children and Adults, we shall have Dr. Louis M. Orr, President of the American Medical Association, Dr. Theodore G. Klumpp, of the A.M.A.'s Committee on Aging, Dr. Edward L. Bortz, Past President of the American Medical Association and a member of the Committee on Aging, and Dr. Ewald W. Busse, Professor of Psychiatry and Chairman of the Committee on Gerontology of the Duke University School of Medicine.

At the Annual Meeting on October 15, our Committee on Aging will report the results of a survey it is now sponsoring to determine the present and future medical needs of the state's aged population. Within the next year or two, data from the recently created Delaware State Citizens' Council on Aging will become available to supplement the Society's survey. This new state agency will be responsible for Delaware's participation in the January, 1961, White House Conference on Aging, and for developing ways and means of pinpointing and solving many medical and social problems of our older citizens. It carried the Society's endorsement, and is in existence largely through the efforts of Dr. Clarence J. Prickett, Chairman of our Committee on Aging. The Council's plans call for participation by physicians on the community level.

Most of us expect the survey of medical facilities for the aged in Delaware to indicate a need for more chronic care beds and/or programs in the foreseeable future. The implications, of course, are greater simply than those of bricks and mortar, should the expectation hold up. We shall be faced, among other things, with the necessity for staffing new facilities and increasing the utilization of our existing facilities.

Dr. Frank G. Dickinson, recently-retired Director of the A.M.A.'s Bureau of Medical Economic Research, expects a "younging" of the population to follow the present trend toward an increasingly older population. He feels that this will be a natural result of the tremendous birth rate since World War II. What we are now faced with apparently is a first wave of aging to be followed in a generation by considerably larger one.

A recent survey by Wayne University of Greater Detroit's senior population is most significant; it has disclosed that nearly two out of five people over sixty-five feel that "the Government should do something." Not unnaturally, the United States Government has felt an obligation to consider these people's demands, although it does not appear that the pressure is particularly heavy for new legislation during the present session of Congress. Certainly the pressure to do something will increase during the years to come.

We have been given relatively little time to provide for our infirm aged, whose problems are at least partially attributable to the rapid progress of twentieth century medicine. In our traditional roles as friends of the sick and as guardians of the future of our profession, I earnestly hope that when you are called on you will actively assist and enthusiastically cooperate with those who are attempting to attack and solve this problem.

Editorials

"DOCTOR T"—

In May 1958, Dr. Tarumianz was honored by the Mental Health Association for forty years of public service to the State of Delaware. More recently a hospital building was named in his honor. These are but small tokens of appreciation and respect for a man who is doing a job so well that there is a tendency to take him for granted.

We are proud of you, Doctor T, and thank you for your part in giving Delaware a good medical reputation at home and abroad.

CONSULTATION OR REFERRAL —

*Procedures in Consultation and Referral** was chosen as the subject for the annual discourse presented to the Massachusetts Medical Society by Dr. Henry F. Howe because he believed that increased courtesy in the conduct of consultations and referrals might, by improving the care of patients, win back some of the respect lost by the medical profession in this generation.

Dr. Howe sent a questionnaire, admittedly clumsy, to 70 fellow physicians, equally divided between general practitioners and specialists; the fact that there were 58 responses is either a tribute to Dr. Howe, an index of the importance of the problem, or both.

The details uncovered in this study can be found in the original article which should be read by specialists as well as non-specialists. Several areas of general misunderstanding, however, were brought to light and these were:

A confusion between the terms "consultation" and "referral". In the former, the attending physician desires the opinion of the consultant regarding the diagnosis and treatment of his patient; this may be accomplished at a single visit although follow-up sessions may be mutually desirable. A "referral" on the other hand means that the patient has been turned over completely to the care of the specialist by the attending physician who no longer has any official status in the case until such time as the patient may be returned to his care. While the attending physicians are loud in their criticism of the specialists on this point, the fact that there is mutual misunderstanding is shown by the specialist's complaint that he frequently is unaware of the attending physician's desire in this matter.

Closely related to this point is that of the report. Many attending physician's complained that the specialist's report was sketchy and incomplete, late, or non-existent. The specialists, on the other hand, complained that many patients reached them with no information whatsoever from the attending physician and that they were faced with the task of trying to discover what the attending physician had in mind when he referred the patient as well as what had been done for the patient in the past.

The other points covered related to reason for consultation, fee splitting, re-referral, responsibility for follow-up care, and case stealing.

It was concluded that given a competent referring physician, a competent consultant, and liberal application of the Golden Rule, misunderstandings would be minimized and good patient care would be the result.

*Howe, H. F.: Annual discourse: procedures in consultation and referral, New England J. Med. 260:1251 (June 18) 1959.

DELAWARE BLUE SHIELD-BLUE CROSS

SENIOR CITIZENS — 65-LIMITED PROGRAM

Realizing the problem confronting families and individuals on the subject of care of the aged, Delaware Blue Cross-Blue Shield, Group Hospital Service has come up with a solution.

Thirty maximum benefit days of hospital coverage plus 30 more at a reduced benefit for each hospital confinement are provided in the new "65-Limited" program.

The benefits are not as extensive as those provided in the standard Blue Cross-Blue Shield contract. There are 14,200 Delawareans 65 years of age or older who already belong to the standard plan and these members may keep this Blue Cross-Blue Shield coverage on reaching age 65. People of long-standing membership should rightfully be provided with the benefits they bought well before they reached the upper age bracket.

There are many people, however—including those who belatedly recognize the need for hospital care, or those who elected other coverage which did not provide continuity of benefits beyond age 65. This new limited program is primarily for these 18,200 Delawareans, 65 or over, who are not members although they may have had previous opportunities to enroll.

Therefore, the following regulation has gone into effect. Employees who apply for Blue Cross-Blue Shield at age 60 or over will become eligible for the benefits of the "65-Limited" Contract *after* leaving any company group of active employees.

The new "65-Limited" program includes hospital-surgical-medical coverage similar to the standard Blue Cross, with these important differences:

1. The new "65-Limited" plan provides 30 days of hospitalization, at $16 a day, plus 30 days at $10 per day, toward all services, for each hospital confinement. The standard semi-private Blue Cross Plan provides 70 days at maximum benefits (the most frequent semi-private accommodations used at the hospital concerned) plus 295 days at $10 per day.

2. Nursing home coverage in the new plan will be 60 days at $8 per day. The standard Blue Cross Plan provides 70 days at the same rate.

3. The new plan provides up to 10 visits by nurses of the Visiting Nurse Association after hospitalization. The standard Blue Cross plan does not include that benefit.

The surgical-medical plan in the "65-Limited" program provides the same benefits as the Blue Shield Plan except that the number of days covered for medical visits in the hospital is reduced from 90 days to 60 days per confinement and no maternity benefits are provided.

Both the new "65-Limited" plan and the standard Blue Shield Plan provide coverage for surgeons' fees up to $225, plus certain payments for anesthesia, x-days and consultations.

The rates for the "65-Limited" program are $6.48 a month for the hospital-surgical-medical coverage for each adult. There is no combined rate for husband and wife; but there is a combined rate of $7.96 per month for hospital-surgical-medical coverage for a subscriber and dependent child (or children) under 19. Subscribers will pay directly to Group Hospital Service.

Enrollment was open during the week of June 22-26, 1959 to all elegible Delawareans in good health, who were not already members of the Blue Cross-Blue Shield Plan. It is anticipated that enrollment for the plan will be offered periodically in the future.

WOMAN'S AUXILIARY

Annual Report of the Kent County Auxiliary to The Delaware State Medical Society, 1958-1959

Kent County records that with its twenty -nine eligible members, organization is one hundred percent. Because of the small membership, efforts have been concentrated mainly on close correlation with the Future Nurses Clubs in all the high schools in Kent County. Necessary information and papers relating to the nurses scholarships have been distributed during the year to the school advisors and school nurses. Late in April, invitations were extended all the Future Nurses Clubs and a tea was held in the Dover High School Cafeteria to promote nursing as a career. A very enlightening film, obtained by the Chairman of Paramedical Careers, was viewed by the girls during the program. It stressed the important role each employee played in his respective field.

Members voted to send two subscriptions of "Today's Health" to the Delaware State Welfare Home at Smyrna and one copy of "Today's Health" to the Kent General Hospital in Dover, for display use in the lobby. These subscriptions were for 4 years each.

The next project was collecting toilet articles and having each member volunteer to assemble a kit, containing hairbrush, cosmetics and toilet articles for distribution at one of the cottages at the Stockley Home for retarded children and adults. The object of this was to help the more advanced patients to care for themselves. Various druggists in Dover and Smyrna contributed cosmetics that were discontinued or damaged and the Coty Corporation of Dover sent a large box of toilet articles and cosmetics. Since ample kits of this kind had already been assembled for Christmas, the extra box of toilet goods was set aside and presented to Dr. Tarumianz at Stockley, right before the Easter holidays.

A gift is presented at Christmas to each girl selected by the organization for a scholarship. This past year, a white orlon sweater was the gift chosen for the scholarship winner from Kent County.

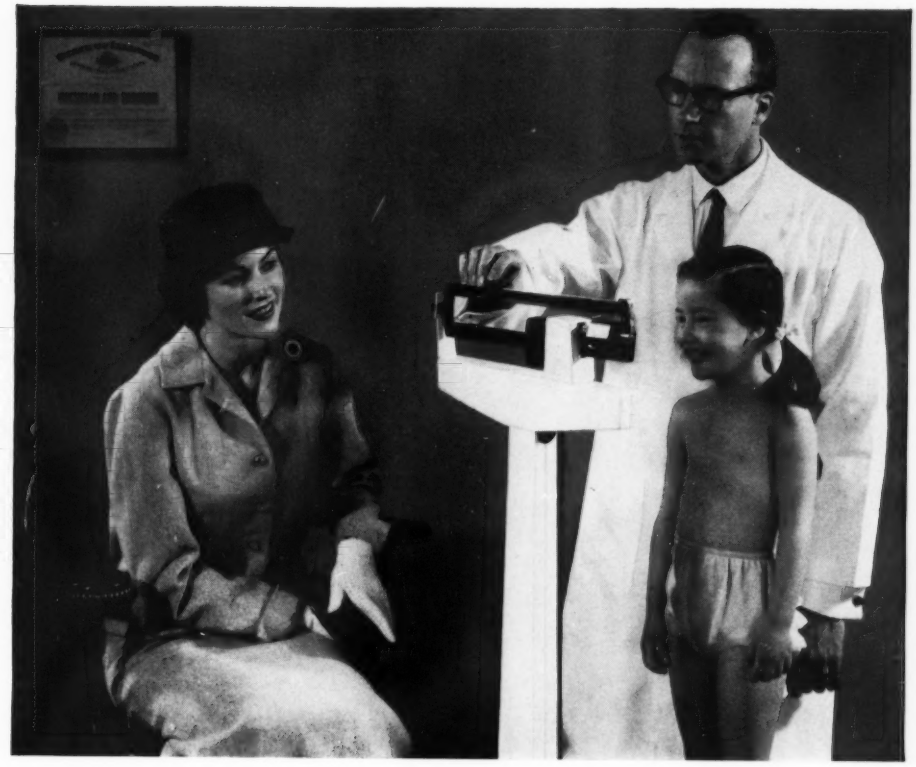
Books, magazines and perodicals or games have been collected and distributed among the patients at the State Welfare Home in Symrna. Members are urged periodically, to drop in for a visit with the old folks who always welcome and appreciate any little thought or remembrance.

A donation was given to the Junior Board of the Kent General Hospital, Dover, to help with the local drive for the newly completed hospital. Many of the members of the Auxiliary helped solicit for the building fund itself. Good attendance at meetings, which only number four per year, has helped in promoting the Auxiliary's projects.

All members have been busy, individually, in other civic projects such as Junior Hospital Board, Girl Scouts and Boy Scouts, PTA, church work and many other organizations that benefit the community.

The Kent County President presents an award from the Auxiliary to each Kent County High School graduate who has made an outstanding contribution to her Future Nurses Club during the year.

MRS. JOHN J. LAZZERI,
President, Kent County Auxiliary



Underweight Children Gain and Retain Weight with Nilevar®

One of the most convincing evidences of the anabolic activity of Nilevar, brand of norethandrolone, has been its ability to improve appetite and increase weight in poorly nourished, underweight children.

A highly important feature of the weight gain thus produced is that it is not ordinarily manifested by deposition of fat but as muscle tissue resulting from the protein anabolism induced by Nilevar.

Anorexia and "Weight Lag" Study—Brown, Libo and Nussbaum have reported* consistent and definite increases in rate of weight gain in eighty-six patients, ranging in age from 7 weeks to 15½ years. This beneficial action of Nilevar was observed in the patients with organic and traumatic disorders as well as those whose only complaints were poor appetite and/or persistent failure to gain weight.

In this study, the weight gained was not lost after discontinuance of Nilevar therapy although many patients did not continue the sharp gains effected by the drug.

The authors are of the opinion that Nilevar is a highly useful anabolic agent for influencing weight gain in underweight children.

When Nilevar is administered to children a dose of 0.25 mg. per pound of body weight is recommended and continuous dosage for more than three months is not recommended.

Nilevar is supplied as tablets of 10 mg., drops of 0.25 mg. per drop and ampuls of 25 mg. in 1 cc. of sesame oil. Further dosage information in Searle Reference Manual No. 4.

G. D. Searle & Co., Chicago 80, Illinois.
Research in the Service of Medicine.

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*Brown, S. S.; Libo, H. W., and Nussbaum, A. H.: Norethandrolone in the Successful Management of Anorexia and "Weight Lag" in Children, Scientific Exhibit presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 20-23, 1958.

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Neo-Synephrine® HCl, 0.5%
– dependable vasoconstrictor and decongestant.

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– antibacterial wetting agent and preservative.

NTZ® **NASAL SPRAY**

Supplied in leakproof, pocket size squeeze bottles of 20 cc.

Winthrop LABORATORIES
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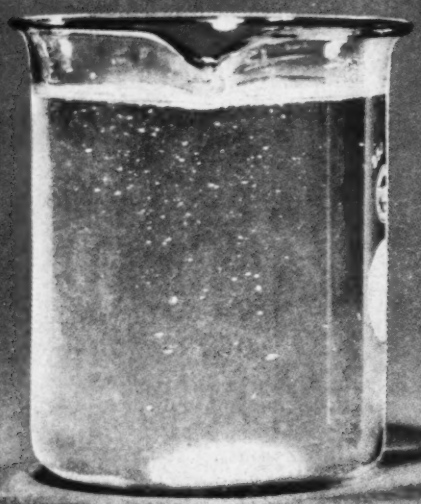
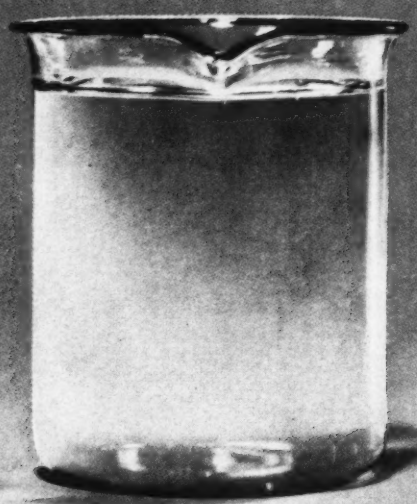
avoid the risk of insoluble, irritating aspirin particles

Chief among the drawbacks to aspirin usage is gastric intolerance. This ranges from mild upset and "heartburn" to severe hemorrhagic gastritis.[1-10] Studies performed in conjunction with gastrectomy[4-6] and gastroscopy[2] have shown insoluble aspirin particles firmly adherent to the gastric mucosa and imbedded between rugae. Reactions varying from mild hyperemia to erosive gastritis have been reported to occur in the areas immediately surrounding these adherent particles.[2-4-5] This is reported to be particularly true in patients with peptic ulcer.[4]

CALURIN is the freely soluble, stable calcium aspirin complex. Its high solubility forestalls gastric irritation or damage



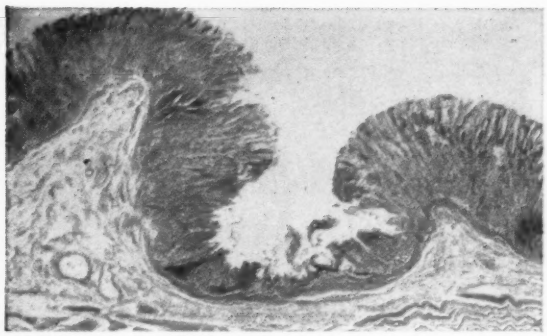
Regular aspirin crystals 24 hours after being mixed into water.



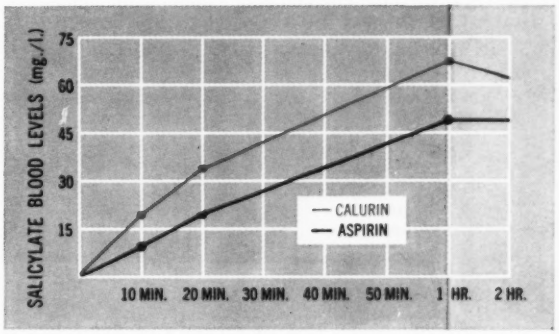
Calurin crystals in solution one minute after being mixed into water.

CALURIN*

STABLE SOLUBLE CALCIUM-ACETYLSALICYLATE-CARBAMIDE



Particle-induced ulceration — section through lesion found in gastrectomy specimen. An aspirin particle was found firmly imbedded in this undermined erosion. Such lesions may be associated with the relative insolubility of aspirin, which remains in particulate form after dispersion in gastric contents.



Calurin, being freely soluble, is promptly available for absorption into the systemic circulation. Salicylate blood levels in 12 subjects receiving both Calurin and plain aspirin were found to rise more than twice as high within ten minutes following Calurin. Also, these levels persisted higher for at least two hours.[11]

CALURIN is the aspirin of choice, especially when high-dosage, long-term therapy is indicated:

1. High solubility forestalls gastric irritation or damage. This advantage is of special importance in arthritis and other conditions requiring high-dosage, long-term therapy.
2. Produces high salicylate blood levels rapidly for prompt analgesic, antipyretic, anti-arthritic effect.
3. Sodium-free – for safer long-term therapy.
4. Flavored: can be chewed or dissolved in the mouth without water if desired – an advantage for patients requiring aspirin administration during the night and for pediatric patients.

Dosage: Each tablet of Calurin is equivalent to 300 mg. (5 gr.) of acetylsalicylic acid. For relief of pain and fever in adult patients, the usual dose of Calurin is 1 to 3 tablets every 4 hours, as needed; in arthritic states, 2 or 3 tablets 3 or 4 times daily; in rheumatic fever, 3 to 5 tablets 4 or 5 times daily. For children over 6 years, the usual dose is 1 tablet every 4 hours; for children 3 to 6 years, ½ tablet every 4 hours, as required. Not recommended for children under 3.

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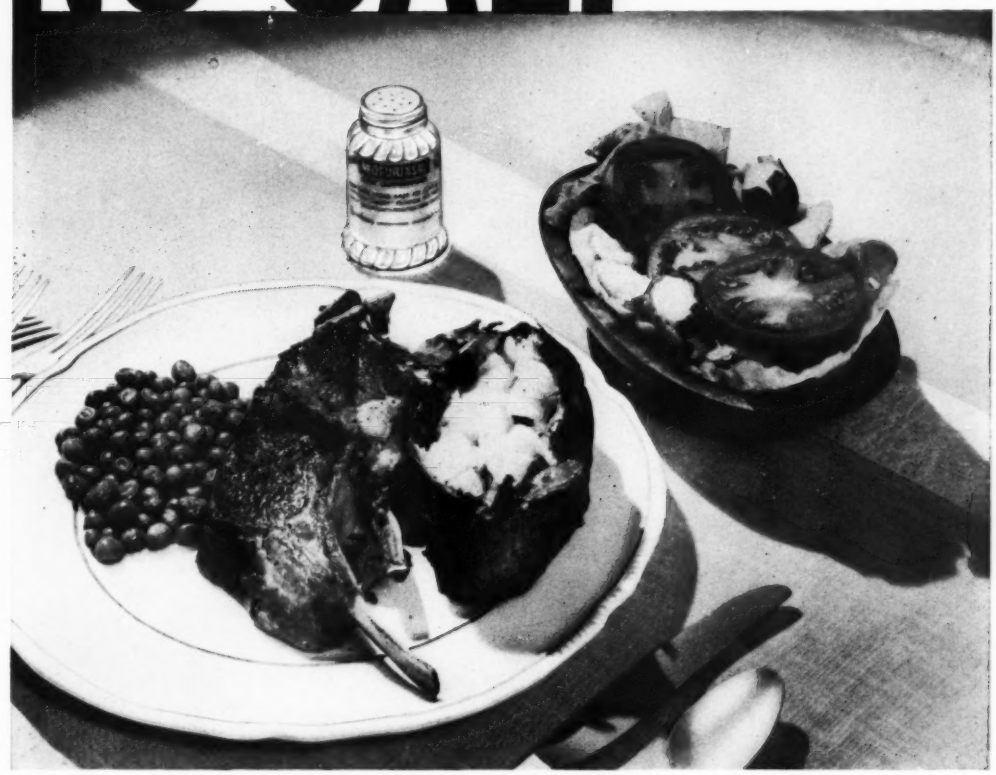

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Contains potassium chloride, potassium glutamate, glutamic acid, calcium silicate, potassium iodide (0.01%).

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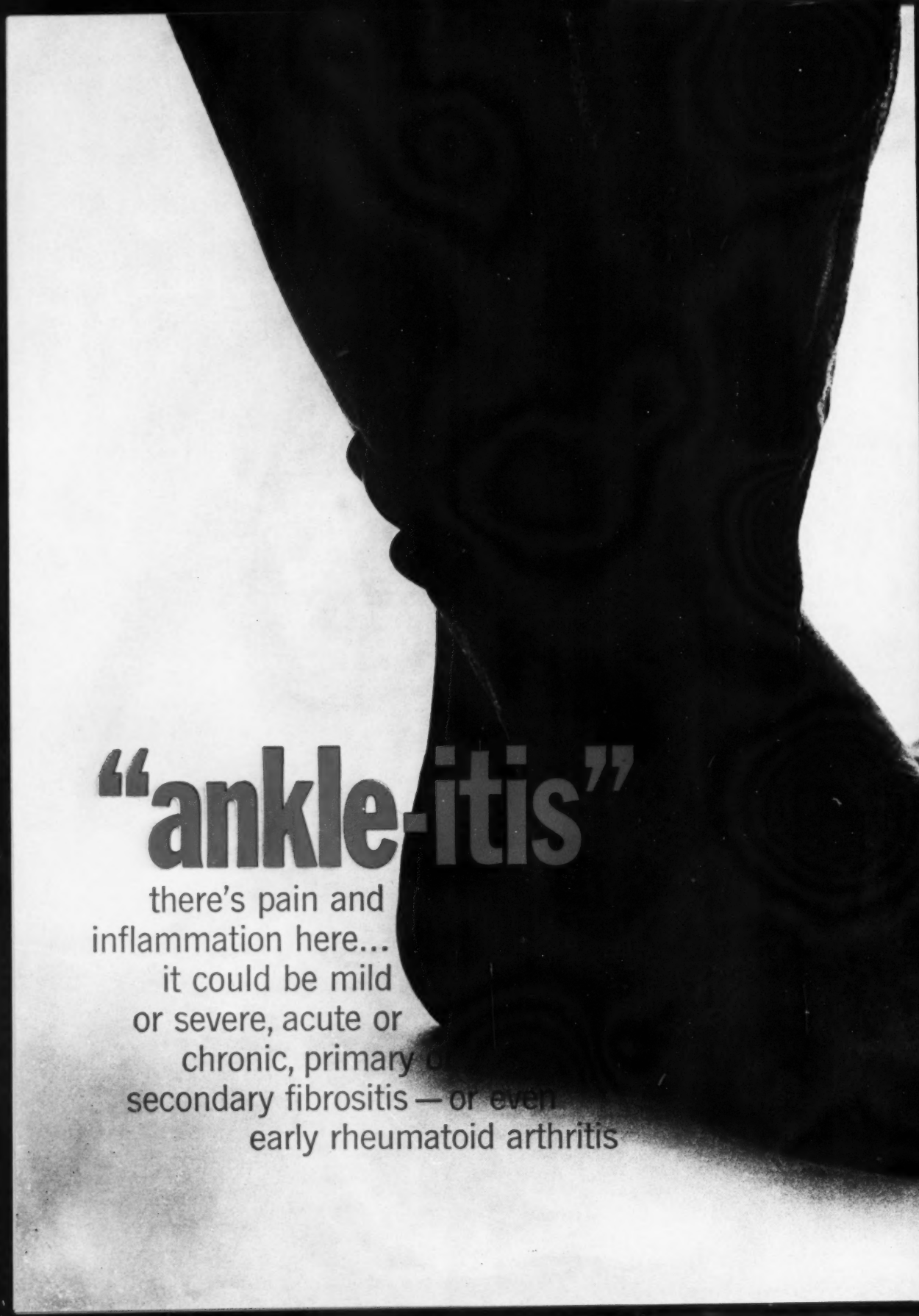
Assures patient's cooperation


"ankle-itis"
there's pain and
inflammation here...
it could be mild
or severe, acute or
chronic, primary
secondary fibrositis — or even
early rheumatoid arthritis

more potent and comprehensive treatment than salicylate alone

. . . assured anti-inflammatory effect of low-dosage corticosteroid[1] . . . additive antirheumatic action of corticosteroid plus salicylate[2-5] brings rapid pain relief; aids restoration of function . . . wide range of application including the entire fibrositis syndrome as well as early or mild rheumatoid arthritis

more conservative and manageable than full-dosage corticosteroid therapy—

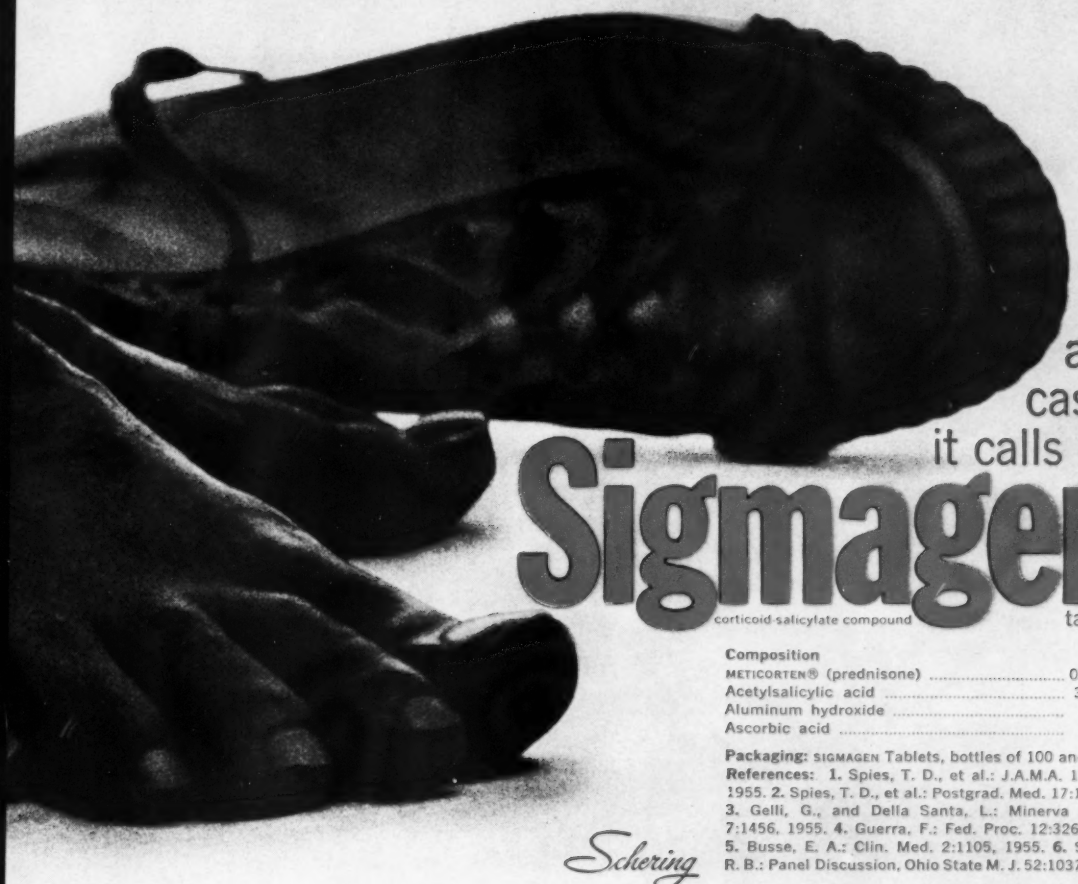
. . . much less likelihood of treatment-interrupting side effects[1-6] . . . reduces possibility of residual injury . . . simple, flexible dosage schedule

THERAPY SHOULD BE INDIVIDUALIZED

acute conditions: Two or three tablets four times daily. After desired response is obtained, gradually reduce daily dosage and then discontinue.

subacute or chronic conditions: Initially as above. When satisfactory control is obtained, gradually reduce the daily dosage to minimum effective maintenance level. For best results administer after meals and at bedtime.

precautions: Because SIGMAGEN contains prednisone, the same precautions and contraindications observed with this steroid apply also to the use of SIGMAGEN.



in any case it calls for

Sigmagen®

corticoid-salicylate compound tablets

Composition

METICORTEN® (prednisone)	0.75 mg.
Acetylsalicylic acid	325 mg.
Aluminum hydroxide	75 mg.
Ascorbic acid	20 mg.

Packaging: SIGMAGEN Tablets, bottles of 100 and 1000.

References: **1.** Spies, T. D., et al.: J.A.M.A. 159:645, 1955. **2.** Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. **3.** Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. **4.** Guerra, F.: Fed. Proc. 12:326, 1953. **5.** Busse, E. A.: Clin. Med. 2:1105, 1955. **6.** Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

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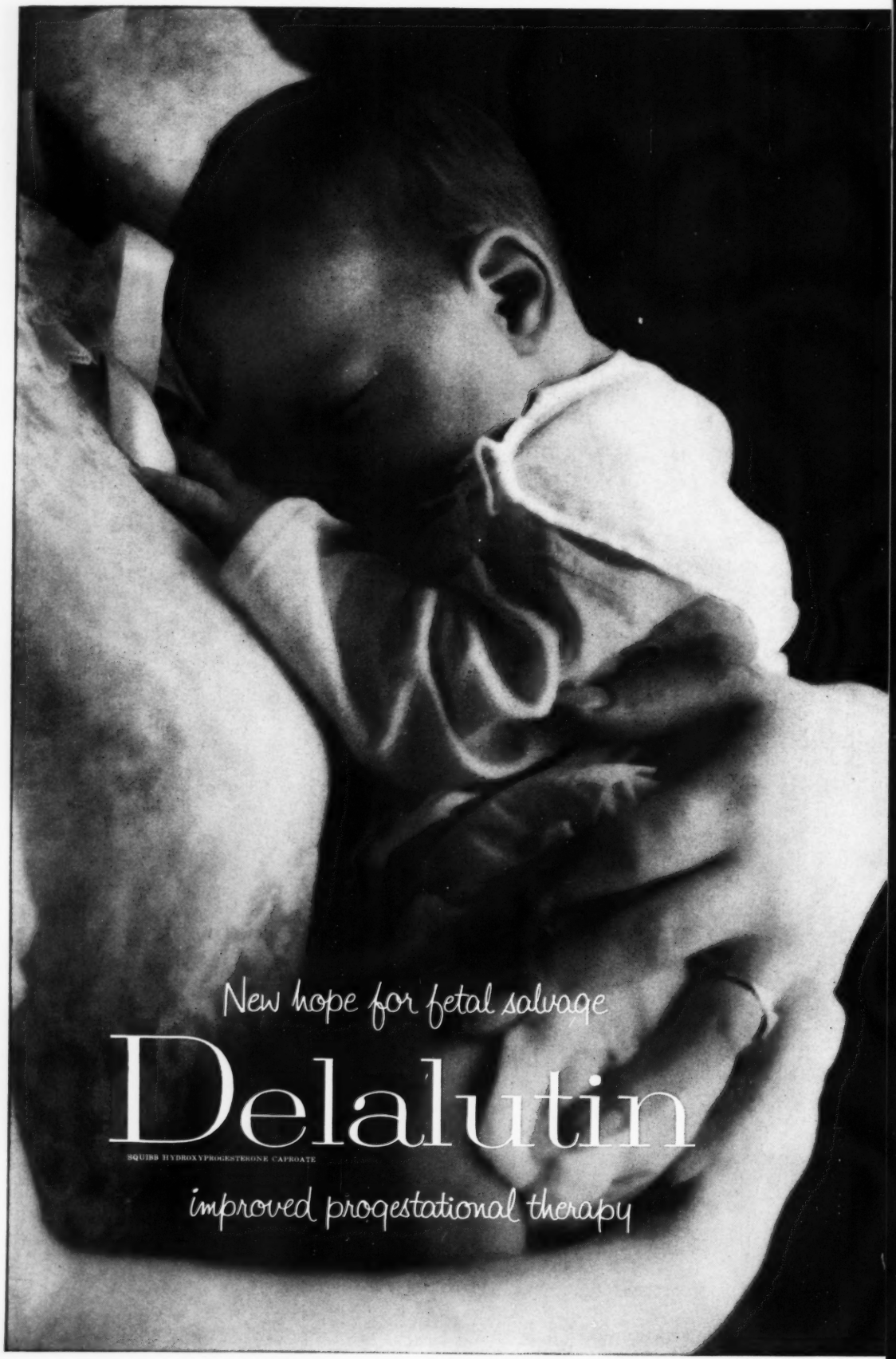
New hope for fetal salvage
Delalutin
SQUIBB HYDROXYPROGESTERONE CAPROATE
improved progestational therapy

The results of administering Delalutin before the 12th week of gestation to 82 women with habitual abortion were reported recently by Reifenstein.[1] Every patient had experienced at least three consecutive abortions immediately preceding the treated pregnancy. More than 68% of these women were delivered successfully and uneventfully following Delalutin therapy.

Boschann,[2] in a study of pregnancies with threatened abortion, found that:

37% of 73 pregnancies were carried to term without progestational therapy
64% of 42 pregnancies were salvaged by progesterone
83% of 73 pregnancies were salvaged by Delalutin

Eichner,[3] found that with Delalutin fetal salvage of infants below term weight (1000 to 2000 gm.) was significantly improved.
108 (76%) of 142 babies of this birth weight survived without progestational therapy.
16 (100%) of 16 babies of this birth weight survived with Delalutin therapy.
A comparison study was made of a group of repeated aborters treated with Delalutin, and a group with a similar history treated with bed rest and sedation.[4] Pregnancy salvage with Delalutin was twice that of the control group. Delalutin was found to be "highly active," well-tolerated and long-acting.

Delalutin offers these advantages over other progestational agents:

- longer-acting and more sustained therapy
- more effective in producing and maintaining a completely matured secretory endometrium
- no androgenic effect
- more concentrated solution requires injection of less vehicle
- unusually well-tolerated, even in large doses
- requires fewer injections
- low viscosity makes administration easier

DELALUTIN is also potent and safe therapy for: threatened abortion; post-partum after-pains; amenorrhea, primary and secondary; dysfunctional uterine bleeding not associated with genital malignancy; infertility with inadequate corpus luteum function; production of secretory endometrium and desquamation during estrogen therapy; premenstrual tension; dysmenorrhea; cyclomastopathy, mastodynia, adenosis and chronic cystic mastitis.

Administration and Dosage: Because of its low viscosity, Delalutin may be administered with a small gauge needle (deep intragluteal injection). Complete information on administration and dosage is supplied in the package insert.

Supply: Delalutin is available in vials of 2 and 10 cc., each cc. containing 125 mg. of hydroxyprogesterone caproate in sesame oil, and benzyl benzoate.

References: 1. Reifenstein, E. C., Jr.: *Annals N. Y. Acad. Sci.* 71:762 (July 30) 1958. 2. Boschann, H-W.: *ibid.*, p. 727. 3. Eichner, E.: *ibid.*, p. 787. 4. Hodgkinson, C. P.; Igna, E. J., and Bukeavich, A. P.: *Am. J. Obst. and Gyn.* 76:279, 1958.

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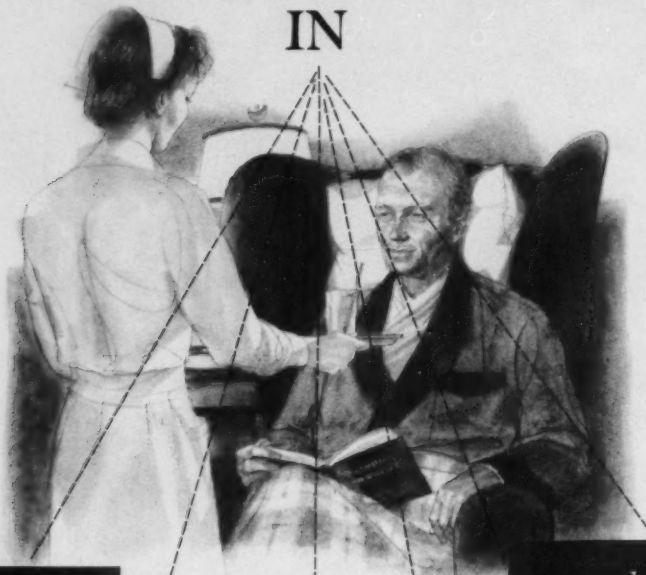

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